DOCKET NO.: 312582US0SD

OBLON
SPIVAK
MCCLELLAND
MAIER
&
NEUSTADT
P.C.

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

ATTENTION: MAIL STOP PATENT TERM EXTENSION

RE: Application Serial No.: 08/295,782
Patentees: Hitoshi NISHIYAMA et al
PCT Filed: March 8, 1993
Patent No.: 5,514,773
Issued: May 7, 1996
For: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF
Group Art Unit: 1811
Examiner: RUSSEL, J. E.

SIR:

Attached hereto for filing are the following papers:

APPLICATION FOR PATENT TERM EXTENSION
WITH EXHIBITS A-H (3 COPIES).

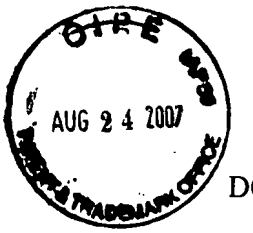
Our credit card payment form in the amount of $1,120.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R §1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. §1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Registration No. 32,884

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)



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U.S. Patent No. 5,514,773
Application for Extension of Patent Term

DOCKET NO: 312582US0 SD

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF	:
HITOSHI NISHIYAMA ET AL	: GROUP ART UNIT: 1811
SERIAL NO: 08/295,782	: EXAMINER: RUSSEL, J. E.
PCT FILED: MARCH 8, 1993	: PATENT NO. 5,514,773
FOR: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF	: ISSUED: MAY 7, 1996

APPLICATION FOR EXTENSION OF PATENT TERM UNDER

35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, AND 1.778

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

08/27/2007 HWUHDHF1 00000015 5514773
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Applicant, Astellas Pharma Inc., of Tokyo, Japan, hereby submits this application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, and 1.778 for U.S. Patent No. 5,514,773 ("the '773 patent").

Applicant, Astellas Pharma Inc., is the assignee of the '773 patent, as evidenced by assignments recorded on October 11, 1994, at Reel/Frame 007276/0013 and on December 12, 2005, at Reel/Frame 017073/0257. Copies of the Patent Assignment Abstract of Title page for the '773 patent and the first assignment are attached hereto as Exhibit A.

The applicant for and the holder of marketing approval for PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution, the approved product which is relevant to

this application, is Bayer HealthCare LLC, Animal Health Division. Bayer HealthCare LLC, Animal Health Division is the exclusive licensee of Astellas Pharma Inc. for the '773 patent. Astellas Pharma Inc. has been authorized by Bayer HealthCare LLC, Animal Health Division to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution. A copy of a letter from Bayer HealthCare LLC, Animal Health Division which authorizes Astellas Pharma Inc. to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution is attached hereto as Exhibit B.

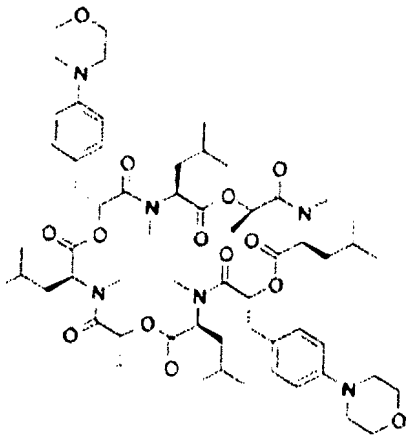
Two additional copies of this application (for a total of three copies) are being submitted herewith (37 C.F.R. § 1.740(b)).

I. Complete Identification of the Product (37 C.F.R. § 1.740(a)(1)).

The approved product is PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution (hereinafter PROFENDER®), which is the registered name for topical solution of lyophilized emodepside and praziquantel. PROFENDER® is a combination product of emodepside and praziquantel for use in the treatment and control of hookworm, roundworm, and tapeworm infections.

Emodepside, a semi-synthetic molecule, is a cyclic depsipeptide. The chemical name for emodepside is cyclo[D-2-hydroxypropanoyl-N-methyl-L-leucyl-2-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl]. Emodepside acts at the neuromuscular junction by stimulating presynaptic receptors

belonging to the secretin receptor family, resulting in paralysis and death of the parasite. The structural formula of emodepside is:



Praziquantel is an isoquinoline cestocide. The chemical name for praziquantel is 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazine-2,1-a-isoquinoline-4-one. A copy of the package insert for PROFENDER® is attached hereto at Exhibit C.

II. Complete Identification of the Federal Statute Underwhich Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell PROFENDER® was granted under 21 U.S.C. § 360(b) (section 512 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of the Date on which the Product Received Approval (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for PROFENDER® was granted under 21 U.S.C. § 360(b) (section 512 of the Federal Food, Drug, and Cosmetic Act) on June 29, 2007, and copy of the approval letter is attached hereto as Exhibit D.

IV. Identification of Each Active Ingredient and Statement that Each Active Ingredient has not been Previously Approved or when Each Active Ingredient was Approved (37 C.F.R. § 1.740(a)(4)).

The approved combination product includes the active ingredients emodepside and praziquantel, and has never been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(A) Emodepside:

Emodepside has not been previously approved for any commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360(e)).

(B) Praziquantel:

Praziquantel has been previously approved for commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360(e)) as indicated by the following information:

1. Alone

NADA number: 111-607

Approval Date: July 16, 1993

For use in dogs and cats for the removal of canine and/or feline cestodes; Dogs: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. Cats: *Taenia taeniaeformis* and *Dipylidium caninum*.

2. Alone

NADA number: 111-798

Approval Date: July, 16, 1993

For use in dogs for the removal of the following canine cestodes: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. For use in cats for the removal of the following feline cestodes: *Dipylidium caninum* and *Taenia taeniaeformis*.

3. Alone

ANADA number: 200-176

Approval Date: October 16, 2002

For use in dogs and cats for the removal of the following canine and/or feline cestodes. Dogs: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and *Echinococcus multilocularis*. Cats: *Taenia taeniaeformis* and *Dipylidium caninum*.

4. Alone

ANADA number: 200-265

Approval Date: August 28, 2003

For use in dogs for the removal of the following canine cestodes: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. For use in cats for the removal of the following feline cestodes: *Dipylidium caninum* and *Taenia taeniaeformis*.

5. With Febantel

NADA number: 133-953

Approval Date: September 12, 1991

For use in dogs and cats for the removal of the following canine and/or feline

nematode parasites: Dogs: Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxocara leonina*), Whipworms (*Trichuris vulpis*), Tapeworms (*Dipylidium caninum* and *Taenia pisiformis*). Cats: Hookworms (*Ancylostoma tubaeforme*), Ascarids (*Toxocara cati*), Tapeworms (*Dipylidium caninum* and *Taenia taeniaeformis*).

6. With Febantel and Pyrantel Pamoate

NADA number: 141-007

Approval Date: February 10, 2003

For use in dogs for the removal of Tapeworms (*Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*), Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxascaris leonina*), and Whipworms (*Trichuris vulpis*).

7. With Ivermectin

NADA number: 141-214

Approval Date: October 28, 2005

For treatment and control of the following parasites in horses: Tapeworms - *Anoplocephala perfoliata*, Large strongyles (adults) - *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus*, *Triodontophorus spp.* including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; Small Strongyles (adults, including those resistant to some benzimidazole class compounds) – *Coronocyclus spp.* including *C. coronatus*, *C. labiatus*, and *C. labratus*, *Cyathostomum spp.* Including *C. catinatum* and *C. pateratum*, *Cylicocyclus spp.* including *C. insigne*, *C. leptostomum*, *C. nassatus*, and *C. brevicapsulatus*, *Cylicodontophorus spp.*, *Cylicostephanus spp.* including *C. calicatus*, *C. goldi*, *C. longibursatus*, and *C. minutus*, and *Petrovinema poculatum*; Small

Strongyles - fourth-stage larvae; Pinworms (adults and fourthstage larvae)-*Oxyuris equi*; Ascarids (adults and third- and fourth-stage larvae)-*Parascaris equorum*; Hairworms (adults)-*Trichostrongylus axei*; Large-mouth Stomach Worms (adults)- *Habronema muscae*; Bots (oral and gastric stages)- *Gasterophilus spp.* including *G. intestinalis* and *G. nasalis*; Lungworms (adults and fourth-stage larvae)-*Dictyocaulus arnfieldi*; Intestinal Threadworms (adults)-*Strongyloides westeri*; Summer Sores caused by *Habronema* and *Draschia spp.* cutaneous third-stage larvae; Dermatitis caused by neck threadworm microfilariae of *Onchocerca sp.*

8. With Ivermectin

NADA number: 141-215

Approval Date: September 16, 2005

For treatment and control of the following parasites in horses:Tapeworms *Anoplocephala perfoliata,* Large Strongyles (adults) *Strongylus vulgaris* (also early forms in blood vessels), *Strongylus edentatus* (also tissue stages), *Strongylus equines, Triodontophorus* spp., Small Strongyles (adults, including those resistant to some benzimidazole class compounds), *Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp., Small Strongyles (fourth-stage larvae), Pinworms (adults and fourth-stage larvae), *Oxyuris equi,* Ascarids (adults and third- and fourth-stage larvae), *Parascaris equorum,* Hairworms (adults), *Trichostrongylus axei,* Large-mouth Stomach Worms (adults), *Habronema muscae,* Bots (oral and gastric stages), *Gasterophilus* spp., Lungworms (adults and fourth-stage larvae), *Dictyocaulus arnfieldi,* Intestinal Threadworms (adults), *Strongyloides westeri,* Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae, Dermatitis caused by Neck threadworm microfilariae, *Onchocerca* sp.

9. With Ivermectin and Pyrantel Pamoate

NADA number: 141-257

Approval Date: October 13, 2006

For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) and for the treatment and control of roundworms (*Toxocara canis*, *Toxascaris leonina*), hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*) and tapeworms (*Dipylidium caninum*, *Taenia pisiformis*).

10. With Pyrantel Pamoate

NADA number: 141-008

Approval Date: September 29, 1993

For use in cats to remove Tapeworms (*Dipylidium caninum, Taenia taeniaeformis*), Hookworms (*Ancylostoma tubaeforme*) and Large Roundworms (*Toxocara cati*).

11. With Moxidectin

NADA number: 141-216

Approval Date: May 14, 2003

For the treatment and control of gastrointestinal parasites of horses and ponies.

V. Statement that Application is being Submitted within the Sixty Day Period (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f), and the last day on which the application could be submitted is August 28, 2007.

VI. Complete Identification of the Patent (37 C.F.R. § 1.740(a)(6)).

The patent for which an extension is being sought is U.S. Patent No. 5,514,773 ("the '773 patent"), which issued May 7, 1996. The inventors listed on the face of the '773 patent are Hitoshi Nishiyama, Masaru Ohgaki, Ryo Yamanishi, and Toshihiko Hara. The '773 patent was filed as a PCT application on March 8, 1993, entered the U.S. national phase on September 12, 1994 (§ 317 date), issued on May 7, 1996, and has an un-extended expiration date of May 7, 2013.

VII. A Copy of the Patent for which Extension of Term is being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '773 patent is attached hereto as Exhibit E.

VIII. Copies of any Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments, or Reexamination Certificates Issued in the Patent (37 C.F.R. § 1.740(a)(8)).

Applicants state on the record that no disclaimers or certificates of correction have been filed or issued in the '773 patent and that no reexamination certificate has been issued in the '773 patent.

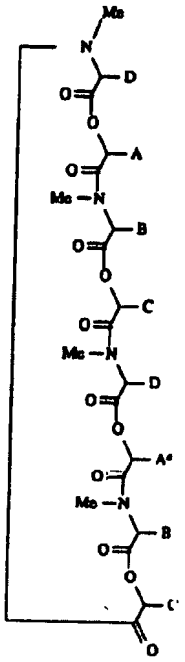
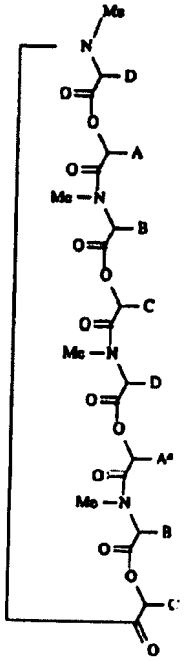
A copy of the receipt of maintenance fee payment for the first maintenance fee in the '773 patent is attached hereto as Exhibit F.

IX. Statement that the Patent Claims the Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, PROFENDER®, is claimed in the '773 patent. Specifically, the '773 patent claims the compound emodepside, itself, and compositions which comprise emodepside. Since PROFENDER® contains emodepside, the claims of the '773 patent cover PROFENDER™.

(A) Claims which Read on the Approved Product (37 C.F.R. § 1.740(a)(9)(i)).

The following chart sets forth the relationship between the approved product and the claims of the '773 patent which read on the approved product.

Claim of the '773 Patent	PROFENDER®
1. A compound of the general formula (I):	PROFENDER® contains emodepside, which has the structure of formula (I):
	

wherein A is a substituted benzyl group or a phenyl group which may have substituent(s), A^a is a benzyl group which may have substituent(s) or a phenyl group which may have substituent(s), B and D are each lower alkyl, and C is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof.	in which A and A^a are each benzyl groups which are substituted with morpholino groups; B and D are both isobutyl groups; and C is a methyl group.
3. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by morpholino, dimethylamino or methoxy.	PROFENDER® contains emodepside, which has the structure of formula (I) in which A and A^a are each benzyl groups which are substituted with morpholino groups.
5. A compound of the formula: [structure omitted].	PROFENDER® contains emodepside, which has the structure of the formula shown in claim 5.
9. An anthelmintic agent which comprises a compound or a pharmaceutically acceptable salt thereof of claim 1 as an active ingredient.	As explained above, PROFENDER® is approved for the treatment of hookworm, roundworm, and tapeworm infections and contains a compound according to Claim 1 of the '773 patent, emodepside.

10. The compound of claim 1 wherein B and D are each an isobutyl group.	PROFENDER® contains emodepside, which has the structure of formula (I) in which B and D are both isobutyl groups.

B. Claims which Read on the Method of Manufacturing the Approved Product (37 C.F.R. § 1.740(a)(9)(iii)).

The following chart sets forth the relationship between the approved product and the claims of the '773 patent which read on the method of manufacturing the approved product.

Claim of the '773 Patent	PROFENDER®
7. A process for preparation of a compound of the general formula: [structure omitted] or a salt thereof, which comprises subjecting a compound of the general formula: [structure omitted] or a salt thereof, to a monoalkylation reaction followed by an intramolecular reaction, wherein B and D are each lower alkyl, C is hydrogen or lower alkyl, A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and A^5 is a benzyl group substituted by cyclic	PROFENDER® contains emodepside, which has the recited structure of the product, in which in which A^5 is a benzyl group which is substituted with a morpholino; B and D are both isobutyl groups; and C is a methyl group.

amino, or a benzyl group substituted by cyclic amino and lower alkoxy.	
12. The process of claim 7 wherein B and D are each an isobutyl group.	PROFENDER® contains emodepside, which has the recited structure of the product, in which in which B and D each an isobutyl groups.

Thus, Claims 1, 3, 5, 9, and 10 cover the approved product itself, while Claims 7 and 12 cover methods of manufacturing the approved product.

X. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) for a Patent Claiming a New Animal Drug (37 C.F.R. § 1.740(a)(10)(ii)).

(A) The Effective Date of the INAD and the INAD number (37 C.F.R. § 1.740(a)(10)(ii)(A)).

The effective date for the INAD (date an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective) for the approved product is June 2, 2000, and the INAD number for the approved product is 10-753.

(B) The Date on which the NADA was Initially Submitted and the NADA Number (37 C.F.R. § 1.740(a)(10)(ii)(B)).

The NADA for the approved product was initially submitted on May 15, 2007, and the NADA number for the approved product is 141-275.

(C) The Date on which the NADA was Approved (37 C.F.R. § 1.740(a)(10)(ii)(C)).

NADA 141-275 was approved on June 29, 2007.

XI. Brief Description of Significant Activities Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period and the Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A list of significant activities undertaken by the marketing applicant during the INAD and the NADA and the significant dates applicable thereto is provided in Table 1 below.

Table 1.

Date To FDA	Date From FDA	Activity
5/30/2000		Request Establishment of an INAD for the Development of an anthelmintic topical solution for cats and kittens. Request for a Development Plan Meeting and submission of the Development Plan.
	6/2/2000	Assign INAD# 10-753
	9/25/2000	A0000; FDA meeting minutes for 7/20/00 Development plan meeting. Granted environmental waiver for INAD.
11/2/2000		Letter responding to FDA's Dev. Plan meeting minutes re: GMP status of starting material.
	12/22/2000	G0001; Letter reconfirming GMP requirement for starting material.
3/16/2001		Submit Model protocol for review - Heartworm disease #151-087
3/16/2001		Submit model protocol for review - immature nematodes #151-076
3/16/2001		Submit model protocol for review - mature nematodes & cestodes #151-078
4/3/2001		Submit "Notice of Intent to Import Clinical Material" to FDA
	6/7/2001	E0004; Protocol Acceptable Letter w/minor comments -mature nematodes/cestodes
	6/21/2001	E0002; Protocol Unacceptable (agreement reached in 7/12 phone call) - Heartworms
	6/21/2001	E0003; Protocol Unacceptable (agreement reached in 7/12 phone call) - Immatures
9/17/2001		Submit 4 safety protocols for review (Dose Tol., Gen.Safety, Oral & HW+ cats)
	11/8/2001	E0006; Safety Protocols (4) submitted 9/17/01 Unacceptable
2/18/2002		Faxed safety questions to CVM concerning 11/8/01 letter
4/9/2002		Resubmitted 4 Safety protocols (Dose Tol., Gen.Safety, Oral & HW+ cats)
4/24/2002		Submitted copy of final signed efficacy protocol #151.086 (T. Taeniaformis)
4/25/2002		Submitted copy of final signed efficacy protocol #141.000 (mature T. cati)
4/25/2002		Submitted copy of final signed efficacy protocol #151.088

		(heartworm)
5/1/2002		Submission of field trial protocol for review (#151.095)
5/1/2002		Submitted copy of final signed efficacy protocol #141.011 (immature A. tubaeforme)
5/1/2002		Submitted copy of final signed efficacy protocol #141.014 (immature T. cati)
5/1/2002		Submitted copy of final signed efficacy protocol #141.710 (E. multilocularis)
5/1/2002		Submitted copy of final signed efficacy protocol #151.076 (immature A. tubaeforme)
5/13/2002		Submitted copy of final signed efficacy protocol #151.077 (mature T. cati)
5/13/2002		Submitted copy of final signed efficacy protocol #151.083 (D. caninum)
6/14/2002		Submitted copy of final signed efficacy protocol #151.084 (D. caninum)
6/14/2002		Submitted copy of final signed efficacy protocol #151.075 (mature A. tubaeforme)
6/14/2002		Submitted copy of final signed efficacy protocol #151.078 (immature T. cati)
6/14/2002		Submitted copy of final signed efficacy protocol #151.085 (T. taeniaeformis)
6/17/2002		Notice of Intent to Import a New Animal Drug for Clinical Trials #2
7/1/2002		Telephone call from Dr. Oeller (CVM reviewer) w/changes to Gen Safety Protocol
7/3/2002		Submitted revised General Kitten Safety Protocol (see 15 & 16 above)
7/8/2002		Submitted copy of final signed efficacy protocol #151.080 (mature T. leonina)
7/8/2002		Submitted copy of final signed efficacy protocol #151.081 (immature T. leonina)
7/8/2002		Submitted copy of final signed efficacy protocol #151.082 (immature T. leonina)
7/12/2002		Submitted copy of final signed efficacy protocol #151.503 (mature A. tubaeforme)
	7/24/2002	E0008, E0025; FDA acceptable letter w/statistical comments on 4 safety protocols (see 33 above)
7/30/2002		Telephone call w/Dr. Luddy (CVM) re: natural infection mature T. leonina study
8/2/2002		Telephone call w/Dr. Luddy (CVM) re: need to do Heartworm+ safety study
	8/5/2002	FDA letter re: review of field trial protocol (see #20 above) - not acceptable
8/6/2002		Submitted copy of final signed efficacy protocol #141.084 (immature T. cati)
8/22/2002		Submitted electronic teleconference request for 9/17 w/ Drs Oeller & Luddy

9/10/2002		Submitted copy of final signed efficacy protocol #141.711 (E. multilocularis)
9/17/2002		Phone Conference Field trial Prot.- Minor corrections, resubmission not needed
	9/26/2002	Z0031;CVM minutes to 9/17/02 phone conference
	11/11/2002	Phone message from Dr. Luddy re: CVM recommendation to do heartworm safety study to allow proper labeling
1/15/2003		E-mail to Dr. Oeller (CVM) re: proposal to change from 3 to 1 dosing on field trial (protocol #151.095)
	1/17/2003	E-mail from Dr. Oeller (CVM) agreeing to change to 1 dosing on field trial 151.095
1/23/2003		Submitted copy of final signed efficacy protocol #151.599 (mature T. leonina)
1/23/2003		Submitted copy of final signed efficacy protocol #151.601 (D. caninum)
1/31/2003		Phone Conversation w/B. Luddy (CVM) re: cat death in study 151.083
2/7/2003		Phone conversation and follow-up e-mail to D. Oeller (CVM) re: 3rd T.cati study
	2/12/2003	E-mail from D. Oeller (CVM) accepting proposal on T. cati - 2 group confirmation study
2/12/2003		Submitted information on cat from study 151.083 per conversation w/B. Luddy 1/31/03
3/10/2003		Submitted copy of final signed efficacy protocol #151.614 (immature T. leonina)
3/10/2003		Submitted copy of final signed efficacy protocol #151.619 (T. cati - natural infections)
3/25/2003		Notice of Intent to Import a New Animal Drug for Clinical Trials #3
4/8/2003		Submitted copy of final signed efficacy protocol #151.629 (mature T. leonina)
6/13/2003		Submitted copy of final signed efficacy protocol #151.640 (mature T. leonina)
8/4/2003		Submitted copy of final signed efficacy protocol #151.652 (T. taeniaeformis)
10/15/2003		Submitted copies of signed protocols 151.095TX1 & MO1 + List of new investigators
10/22/2003		Submitted copy of signed field trial protocol (151.095-SC)
11/10/2003		Submitted copy of signed field trial protocol (151.095-VA)
12/29/2003		CMC Phased Technical Section submitted to CVM
1/7/2004		Update meeting with CVM on Safety & Efficacy
1/26/2004		Submitted copy of signed field trial protocol (151.095-ON)
1/29/2004		Submitted Copy of signed field trial protocol (151.095-BC)
3/24/2004		Submitted copy of final signed efficacy protocol #151.732 (immature/adult) T. leonina
3/24/2004		Submitted copy of final signed efficacy protocol #151.733 (immature/adult) T. leonina
3/25/2004		Submitted Environmental Assessment waiver request

	5/6/2004	CVM letter approving Environmental Technical Section submitted 3/25/04
	6/30/2004	CVM incomplete letter on 29 Dec03 CMC Tech Section submission
3/29/2004		Submission of Information concerning ADE in field trial (151.095-SC)
6/28/2004		Submission of Phased Target Animal Safety Section (27 Volumes)
9/27/2004		Submission of Phased Effectiveness Technical Section (86 Volumes)
11/9/2004		Amendment 1 to Phased Safety Section (s:6/28/04) - data spreadsheets for 4 pivotal studies
	12/04 - 4/05	Various calls from CVM reviewer Cacia Masser with questions concerning Efficacy data
2/15/2005		Response submitted to CVM 6/30/04 CMC incomplete letter
2/17/2005		Amendment #1 to 27SEP04 Phased Efficacy Section - to formally submit information previously provided to reviewer by email
3/3/2005		Amendment #2 to 27SEP04 Phased Efficacy Tech. Section - copies of emails between Bayer and CVM concerning efficacy discussions during review
	4/28/2005	CVM incomplete letter on 28JUN04 Safety Tech Section submission
	8/5/2005	CVM Technical Section Complete Letter for 27SEP04 Efficacy submission
	8/9/2005	2nd CVM CMC incomplete letter on 2/15/04 CMC response
	7/14-28/2005	3 phone calls from CVM with questions on efficacy data and FOI
2/22/2006		Sent Histopathology slides to CVM for review as part of Safety response
2/23/2006		Response submitted to 28APR05 Safety Tech. Section incomplete letter
3/30/2006		Response to 2nd CVM CMC incomplete letter dated 9AUG05
	6/06-10/9/06	Various calls from CVM reviewer Ann Stohlman with questions concerning safety submission/FOI
7/20/2006		Amendment #1 to 23FEB06 Safety Tech. Section response - complete copies of several references
	9/28/2006	CMC Tech. Section complete Letter (I-0101753-P-0094) for 29DEC03 Tech Section as amended
10/3/2006		Conversation w/Dr. Dennis Bensley (CVM) about statements in CMC complete letter. New requirement for foreign manufacturing sites - final product validation report and protocol must be submitted prior tp distributing product.
	10/13/2006	CVM Safety Technical Section complete Letter for 28JUN04 Tech Section as amended
	10/17/2006	Histology slides (sent 2/22/06) returned to Bayer and on to Stillwell
10/19/2006		Conversation between Bruce Martin and Dr. Steve Vaughn (CVM) concerning Bayer's plan to add "pregnant woman"

		warning statement to label.
12/13/2006		"All Other Information" Minor Technical Section is submitted
12/22/2006		"Labeling" Minor Technical Section is submitted
1/5/2007		Amendment #1 to "All Other Info" Tech. Section - abstract of Japanese Field trial
2/07 - 4/07		Various calls from CVM reviewer Ann Stohlman with questions concerning Labeling/FOI & All Other Info
4/12/2007		Amendment #2 to "All Other Info" Tech. Section - Draft of 3rd PSUR
4/13/2007		Amendment #3 to "All Other Info" Tech. Section - Copy of report referenced in 3rd PSUR ("Comparative in vitro Dermal Absorption using Human and Rat Skin").
	4/23/2007	"All Other Information" Tech. Section complete Letter (I-0101753-M-0096) for 13DEC06 Tech Section as amended
4/25/2007		Amendment #1 to 22DEC06 "Labeling" Tech. Section - revised facsimile labeling
	5/2/2007	CVM telephone call requesting final label changes
5/3/2007		Amendment #2 to 22DEC06 "Labeling" Tech. Section - revised facsimile labeling
	5/9/2007	FOI Summary Tech. Section complete Letter (I-0101753-Q-0098) with final FOI Summary attached
	5/11/2007	Labeling Tech. Section complete Letter (I-0101753-M-0097) for 22DEC06 Tech Section as amended
5/15/2007		Administrative NADA submitted to CVM
	5/18/2007	Letter received from CVM DocCenter assigning NADA number 141-275
5/30/2007		Amendment #1 to Administrative NADA submitted after telephone call with CVM concerning a spelling error on all 3 cartons
6/4/2007		Amendment #2 to Administrative NADA submitted after telephone call with CVM concerning a spelling error on all 3 cartons
	6/8/2007	Call from CVM requesting a correction to the ADVERSE REACTION section of the product insert.
6/8/2007		Amendment #3 to Administrative NADA submitting revised insert per CVM request.
	6/29/2007	CVM letter approving original new animal drug application NADA 141-275 for Profender

XII. Statement that in the Opinion of the Applicant the Patent is Eligible for Extension of Patent Term and Statement as to the Length of extension and how the Length was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the applicant, the '773 patent is eligible for extension. In the opinion of the applicant, the '773 patent is entitled to be extended by 1314 days, *i.e.*, the '773 patent is entitled to an extended expiration date of December 11, 2016. The extension was calculated by the method described in 37 C.F.R. § 1.778.

The number of days by which the '773 patent should be extended was calculated as follows:

A. The minimum number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.778(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.778(d)(1)-(6).

B. The minimum number of days in the regulatory review was calculated by adding the number of days pursuant to (37 C.F.R. § 1.778(c)(1)) and the minimum number of days pursuant to (37 C.F.R. § 1.778(c)(2)).

C. The number of days pursuant to (37 C.F.R. § 1.778(c)(1)) was calculated as the number of days in the period starting from the date on which INAD 10-753 was approved, June 2, 2000, and ending on the date NADA 141-275 was submitted, May 15, 2007, and determined to be 2538 days.

D. The minimum number of days pursuant to (37 C.F.R. § 1.778(c)(2)) was calculated as the number of days in the period starting from the date NADA 141-275 was submitted, May 15, 2007, and ending on the date of approval of NADA 141-275, June 29, 2007, and determined to be at least 45 days.

E. Thus, the minimum number of days in the regulatory review period under 37 C.F.R. § 1.778(c) was calculated by adding 2538 days to 45 days and determined to be 2583 days

F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.778(d)(1) was calculated by determining the number of days pursuant to each of C.F.R. §§ 1.778(d)(1)(i)-(iii).

G. Since the regulatory review period began on June 2, 2000, and since the '773 patent issued on May 7, 1996, 0 days in the regulatory review period were on or before the date on which the '773 patent issued. Thus, the number of days pursuant to C.F.R. § 1.778(d)(1)(i) was determined to be 0.

H. As set forth above, applicants have acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to C.F.R. § 1.778(d)(1)(ii) was determined to be 0.

I. The number of days pursuant to C.F.R. § 1.778(d)(1)(iii) was calculated by first subtracting the number of days pursuant to C.F.R. § 1.778(d)(1)(i), 0 days, from the number of days pursuant to 37 C.F.R. § 1.778(c)(1), 2538 days, to obtain 2538 days and then dividing that number of day in half and determined to be 1269 days.

J. The number of days pursuant to C.F.R. § 1.778(d)(1) was calculated by subtracting the number of days calculated pursuant to C.F.R. § 1.778(d)(1)(i), 0 days, and the number of days calculated pursuant to C.F.R. § 1.778(d)(1)(iii), 1269 days, from the number of days calculated pursuant to C.F.R. § 1.778(c), 2583 days, and determined to be 1314 days.

K. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(2) was calculated by adding the number of days calculated pursuant to C.F.R. § 1.778(d)(1), 1314 days, to the original term of the '773 patent (current expiration date May 7, 2013) and determined to be December 11, 2016.

L. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(3) was calculated by adding 14 years to the date of approval, June 29, 2007, and determined to be June 29, 2021.

M. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(4) was calculated by comparing the dates calculated pursuant to C.F.R. § 1.778(d)(3) and C.F.R. § 1.778(d)(4) and selecting the earlier date and determined to be December 11, 2016

N. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(5)(i) was calculated by adding five years to the original expiration date of the '773 patent (May 7, 2013) and determined to be May 7, 2018.

O. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(5)(ii) was calculated by selecting the earlier date pursuant to C.F.R. § 1.778(d)(4) and C.F.R. § 1.778(d)(5)(i) and determined to be December 11, 2016.

P. Since the '773 patent issued after November 16, 1988, no adjustment was made under C.F.R. § 1.778(d)(6).

XIII. Statement that Applicant Acknowledges a Duty to Disclose any Information which is Material to the Determination of the Entitlement to the Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such, must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension

proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

XIV. Prescribed Fee (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j)(1) is attached hereto in the from of a credit card form for the amount of $1,120.00.

XV. Correspondence Information (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Power of Attorney (37 C.F.R. §§ 1.730(a)(2) and (d)).

A copy of the original Power of Attorney is being submitted herewith as Exhibit G.

As can be seen from the face of the '773 patent itself, the '773 patent was originally assigned to Fujisawa Pharmaceutical Co., Ltd., of Osaka, Japan ("Fujisawa"). Effective April 1, 2005, Fujiswa became part of Astellas Pharma Inc., of Tokyo, Japan. A formal notice of the change of name has already been filed in the USPTO, and copies of the papers filed are attached hereto as Exhibit H. Oblon, Spivak, McClelland, Maier & Neustadt, P.C., remains the attorney of record for the '773 patent.

In view of the foregoing, Applicants submit that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 5514773 **Issue Dt:** 05/07/1996 **Application #:** 08295782 **Filing Dt:** 09/12/1994

Inventors: HITOSHI NISHIYAMA, MASARU OHGAKI, RYO YAMANISHI, TOSHIHIKO HARA

Title: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF

Assignment: 1

Reel/Frame: 007276/0013 **Recorded:** 10/11/1994 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: NISHIYAMA, HITOSHI **Exec Dt:** 08/05/1994

OHGAKI, MASARU **Exec Dt:** 08/05/1994

YAMANISHI, RYO **Exec Dt:** 08/05/1994

HARA, TOSHIHIKO **Exec Dt:** 08/05/1994

Assignee: FUJISAWA PHARMACEUTICAL CO., LTD.
4-7, DOSHOMACHI 3-CHOME, CHUO-KU
OSAKA-SHI, OSAKA 541, JAPAN

Correspondent: NORMAN F. OBLON
OBLON, SPIVAK, MCCLELLAND ET AL.
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

Assignment: 2

Reel/Frame: 017073/0257 **Recorded:** 12/12/2005 **Pages:** 39

Conveyance: MERGER (SEE DOCUMENT FOR DETAILS).

Assignor: FUJISAWA PHARMACEUTICAL CO., LTD. **Exec Dt:** 04/01/2005

Assignee: ASTELLAS PHARMA INC.
3-11, NIHONBASHI-HONCHO 2-CHOME
CHUO-KU, TOKYO, JAPAN

Correspondent: OBLON, SPIVAK, MCCLELLAND, MAIER & NEUST
1940 DUKE STREET
ALEXANDRIA, VA 22314

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1-31-92

79 Rec'd PCT/PTC 11 OCT 1994

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U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Hitoshi NISHIYAMA
Masaru OHGAKI
Ryo YAMANISHI
Toshihiko HARA

Additional name(s) of conveying party(ies) attached? –☐ Yes –■ No

2. Name and address of receiving party(ies):

Name: FUJISAWA PHARMACEUTICAL CO., LTD.

Address: 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi
Osaka 541, JAPAN

Additional name(s) & address(es) attached? –☐ Yes –■ No

3. Nature of Conveyance:

19

–■ Assignment –☐ Merger
–☐ Security Agreement –☐ Change of Name
–☐ Other _____

Execution Date: August 5, 1994

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

08/295,782

B. Patent No.(s)

Additional numbers attached? –☐ Yes ■ No

95 JAN 25 PM 4:53
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ASSIGNMENT BRANCH

5. Name and address of party to whom correspondence concerning document should be mailed:

Norman F. Oblon
OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
Attorneys at Law
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $40.00

■ Enclosed
–☐ Authorized to be charged to deposit account

8. Deposit account number: 15-0030

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Norman F. Oblon
Name of Person Signing

Robert F. Gnuse
Registration Number 27,295
Signature

10/6/94
Date

Total number of pages comprising cover sheet: 3

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93734414

Assignment Of Application

WHEREAS, I (WE) Hitoshi Nishiyama, Masaru Ohgaki, Ryo Yamanishi and Toshihiko Hara

INSERT NAMES AND RESIDENCE ADDRESSES OF THE INVENTORS:

of 13-1-317, Kuzuharshinmachi, Neyagawa-shi, OSAKA 572 JAPAN; 3-1-58-506, Minatojimanakamachi, Chuo-ku, Kobe-shi, HYOGO 650 JAPAN, 16-3, Hoshimi-cho, Ibaraki-shi, OSAKA 567 JAPAN and 565-19, Ooaza Miyaji, Miura-mura, Inashiki-gun, IBARAKI 300-04 JAPAN

, respectively,

INSERT TITLE OF INVENTION:

have invented certain new and useful improvements in: DEPSIPEPTIDE DERIVATIVE, PRODUCTION THEREOF AND USE THEREOF,

INSERT DATE INVENTORS SIGNED DECLARATION:

for which an application for Letters Patent was executed on August 5, 1994

(Application No. 08/295,782, filed September 12, 1994), and

INSERT NAME AND ADDRESS OF COMPANY OR OTHER ASSIGNEE:

WHEREAS, Fujisawa Pharmaceutical Co., Ltd.

(hereinafter referred to as "ASSIGNEE") having a place of business at: 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, OSAKA 541 JAPAN,

is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefore in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letter Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Spivak, McClelland, Maier & Neustadt, P.C. of Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

Date: August 5, 1994 — Hitoshi Nishiyama (Signature of Inventor) Hitoshi Nishiyama

Date: August 5, 1994 — Masaru Ohgaki (Signature of Inventor) Masaru Ohgaki

Date: August 5, 1994 — Ryo Yamanishi (Signature of Inventor) Ryo Yamanishi

Date: August 5, 1994 — Toshihiko Hara (Signature of Inventor) Toshihiko Hara

Date: _____ (Signature of Inventor) _____

Date: _____ (Signature of Inventor) _____

Date: _____ (Signature of Inventor) _____

Date: _____ (Signature of Inventor) _____

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OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

Bayer HealthCare
Animal Health

Ms. Mary Till
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Jessica Monachello
Patent Counsel

Re: Application for Patent Term Extension For U.S. Patent No. 5,514,773

August 21, 2007

Dear Ms. Till:

Bayer HealthCare LLC, Animal Health Division is the applicant for and the holder of marketing approval for PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution (hereinafter PROFENDER®). Bayer HealthCare LLC, Animal Health Division authorizes Astellas Pharma Inc. to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® for the extension of the term of U.S. Patent No. 5,514,773.

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201

Phone: 913-268-2038
Fax: 913-268-2855
jessica.monachello.b@bayer.com

Very truly yours,

Jessica Monachello

Jessica J. Monachello

cc: Cynthia Hughes-Coons
Assistant General Counsel

Topical Solution

Profender.

(emodepside/praziquantel)

CAUTION: Federal law (U.S.A.) restricts this drug to use by or on the order of a licensed veterinarian.

Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections in cats and kittens that are at least 8 weeks of age and weigh at least 2.2 lbs (1 kg).

DESCRIPTION:

PROFENDER [1.98% emodepside/7.94% praziquantel] Topical Solution is a clear yellow ready-to-use solution packaged in single unit dosing applicator tubes for topical (dermal) treatment of cats 8 weeks of age and older and weighing at least 2.2 lbs (1 kg). The formulation and dosage schedule is designed to provide a minimum of 1.36 mg/lb (3 mg/kg) emodepside and 5.45 mg/lb (12 mg/kg) praziquantel based on body weight.

Emodepside, a semi-synthetic molecule, is a cyclic depsipeptide. The chemical name is Cyclo [D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl].

Praziquantel is an isoquinoline coumicide. The chemical name is 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino-2,1-a-isoquinolin-4-one.

INDICATIONS:

PROFENDER Topical Solution is indicated for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats.

DOSAGE AND ADMINISTRATION:

The recommended minimum dose is 1.36 mg/lb (3 mg/kg) emodepside + 5.45 mg/lb (12 mg/kg) praziquantel as a single topical dose. A single treatment is effective and a second treatment should not be necessary. If re-infection occurs, the product can be re-applied after 30 days.

1. Select the package that correctly corresponds with the body weight of the cat. (See Table below.)

Cat Weight*	Package Size/Color	Volume (ml)	Up to 2 Packages	Up to 4 Packages
2.2-5 lbs	Small	0.35	1:1	1:2
>5.5-10 lbs	Medium	0.70	2:3	4:5
>10.5-15 lbs	Large	1.12	3:4	8:1

* Cats over 17.6 lbs should be treated with the appropriate combination of tubes.

2. Remove one unit dose tube from the package.
3. While holding the tube in an upright position, pull the cap off the tube.
4. Turn the cap over and place the other end of cap onto the tip of the tube.
5. Twist the cap to break the seal and then remove cap from the tube.

6. Part the hair on the back of the cat's neck at the base of the head, until the skin is visible.

7. To ensure the entire contents of the tube are administered, place the tip of the tube on the skin and squeeze the entire contents directly onto the skin. Lift tube away from the skin before releasing pressure on the tube. Do not allow the cat to lick the application site.

Do not apply to broken skin or if hair coat is wet. Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for one hour. Oral exposure can cause salivation and vomiting. Treatment at the base of the head will minimize the opportunity for ingestion while grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff hair, a damp appearance of the hair, or a slight powdery residue may be observed at the treatment site. These effects are temporary and do not affect the safety or effectiveness of the product.

HUMAN WARNINGS:

Not for human use. Keep out of reach of children.

To prevent accidental ingestion of the product, children should not come in contact with the application site for twenty-four (24) hours while the product is being absorbed. Pregnant women, or women who may become pregnant, should avoid direct contact with, or wear disposable gloves when applying, this product. Studies performed in rats and rabbits suggest that emodepside may interfere with fetal development in those species.

PROFENDER topical solution may be irritating to skin and eyes. Reactions such as facial, tongue and hand swelling have been reported in humans in rare instances. Avoid contact with the application area while it is wet and wash hands thoroughly with soap and warm water after handling. People with known hypersensitivity to butylhydroxytoluene, emodepside or praziquantel should administer the product with caution. If the product accidentally gets into eyes, flush thoroughly with water. May be harmful if

Bayer HealthCare

Profender® Topical Solution (emodepside/praziquantel)

Multiple Insert Proof

swallowed. In case of accidental ingestion or if skin or eye irritation occurs, call a poison control center or physician for treatment advice.

The Material Safety Data Sheet (MSDS) provides additional occupational safety information. For customer service or to obtain product information, including the MSDS, call 1-800-633-3796. For medical emergencies or to report an adverse reaction, call 1-800-422-9874.

PRECAUTIONS:

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.3 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See Animal Safety.)

ADVERSE REACTIONS:

Field study: In a controlled, double-masked field safety study, owners administered PROFENDER Topical Solution to 606 cats. Adverse reactions reported by the cat owners included flicking/excessive grooming in 18 cats (3.0%), scratching treatment site in 15 cats (2.5%), salivation in 10 cats (1.7%), alopecia in 8 cats (1.3%), agitation/nervousness in 7 cats (1.2%), vomiting in 6 cats (1.0%), diarrhea in 3 cats (0.5%), eye irritation in 3 cats (0.5%), respiratory irritation in 1 cat (0.2%) and shaking/tremors in 1 cat (0.2%). All adverse reactions were self-limiting.

Laboratory effectiveness studies: One cat died 10 days after receiving PROFENDER Topical Solution. The necropsy showed chronic active cholangiohepatitis. While the use of the drug did not appear to be the direct cause of death, treatment with the drug cannot be ruled out as a contributing factor (See PRECAUTIONS). One cat treated with a vehicle placebo (formulation minus the active ingredients) showed salivation, gagging, lethargy and a swollen tongue.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in foreign markets: application site reaction (hair loss, dermatitis, pyoderma, edema, and erythema), salivation, pruritus, lethargy, vomiting, diarrhea, dehydration, ataxia, loss of appetite, facial swelling, rear leg paresis, seizures, hyperesthesia, twitching, and death.

EFFECTIVENESS:

In a total of 13 controlled laboratory studies to establish effectiveness, 149 cats were treated with PROFENDER Topical Solution. In the field study conducted at 13 veterinary clinics/hospitals, 637 purebred or crossbred cats from single and multi-cat households were enrolled to evaluate safety and effectiveness under field conditions of use. Of these, 606 received a single treatment with PROFENDER Topical Solution. Cats ranged between 2 months and 17 years of age and weighed between 0.8 lbs (0.36 kg) to 21 lbs (9.47 kg). Data from these studies demonstrated PROFENDER Topical Solution is safe and effective for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults).

ANIMAL SAFETY:

In a field study, PROFENDER Topical Solution was used in cats receiving other frequently used products including analgesics, anti-fungals, non-steroidal anti-inflammatories, anthelmintics, antiadrenergics, flea and tick products, sedatives, anesthetics, cardiac medications, antiemetics, hormonal treatments, steroids, otic and ophthalmic preparations, and vaccines.

Dose Tolerance Study in Cats: PROFENDER Topical Solution was applied topically one time to young cats at 10X the recommended label use rate. Two cats salivated. Another cat exhibited tremors and lethargy. These signs were self-limiting.

Oral Safety Studies in Cats: PROFENDER Topical Solution was administered orally at the recommended topical dose to young adult cats. The cats exhibited salivation, vomiting, tremors, abnormal gait, abnormal respiration and weight loss. These signs were self-limiting.

General Safety Study in Kittens: PROFENDER Topical Solution was topically applied at 0X (vehicle control), 1X, 3X and 5X the maximum dose to 48 healthy 8-week-old kittens every two weeks for six doses. One 5X kitten experienced salivation and tremors and another 5X kitten experienced salivation on the day of dosing. A third 5X kitten experienced tremors the day after dosing. These cats vomited within 24 hours of dosing, one each in vehicle control, 3X and 5X groups.

Safety Study in Heartworm Positive Cats: Cats artificially infected with adult heartworms harvested from dogs were treated topically with PROFENDER Topical Solution at 0X, 1X or 5X the recommended dose once a month for three treatments. Clinical signs included salivation (one 1X and three 5X cats), labored breathing (all groups) and lethargy (one 5X cat). At the study conclusion, the 1X and 5X cats had fewer live heartworms recovered than the 0X group.

STORAGE INFORMATION:

Store at or below 77°F (25°C).
Protect from freezing.

HOW SUPPLIED:

Code Number	Application per Package
03615028	4D - 0.35 mL tubes (10 blisters of 4 tubes)
03615034	4G - 0.70 mL tubes (10 blisters of 4 tubes)
03615042	2M - 1.12 mL tubes (5 blisters of 4 tubes)

Profender is protected by the following U.S. Patents: 5 514 773, 5 589 503, and other patents pending.

Made in Germany

NADA #XXX-XXX, Approved by FDA

Bayer, the Bayer Cross and Profender are trademarks of Bayer.

03615028/03615034/03615042, R.0
April, 2007

Bayer HealthCare

Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 U.S.A.

Profender® Topical Solution
(emodepside/praziquantel)
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Back

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

N-141275-A-0000-OT

JUN 29 2007

Bayer HealthCare LLC
Animal Health Division
Attention: Pam Triplett
Senior Regulatory Affairs Consultant
P.O. Box 390
Shawnee Mission, KS 66201

Re: Request for original approval of PROFENDER Topical Solution

Dear Ms. Triplett:

We approve your original new animal drug application (NADA) for PROFENDER Topical Solution dated May 15, 2007, amended on May 30, 2007, June 4, 2007, and June 8, 2007. Emodepside and praziquantel topical solution is approved for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats. The expiration dating for this drug is 24 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. Any request to change the conditions of this approval may require the submission of a supplemental application.

PROFENDER Topical Solution, as approved in this letter, qualifies for THREE years of marketing exclusivity beginning as of the date of this letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. §360b(c)(2)(F)(ii)).

Your final printed labeling should be identical to the facsimile labeling submitted May 15, 2007 (A-0000), for the tube labels, blister packs, and shipping labels, June 4, 2007 (M-0002), for the display cartons, and June 8, 2007 (M-0003), for the package insert. You should submit three copies of each component of the final printed labeling to CVM before distributing and marketing the drug product.

Under good manufacturing practices (GMPs) (21 CFR Parts 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the

drug product. A product that does not conform to GMPs is adulterated under section 501(a)(1)(B) of the act (21 U.S.C. §351(a)(1)(B)).

If you submit correspondence relating to this approval, you should reference this letter by date and the alphanumeric identifier found at the top of this letter. If you have any questions, please contact Dr. Melanie R. Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary

US005514773A

United States Patent [19]

Nishiyama et al.

[11] Patent Number: 5,514,773

[45] Date of Patent: May 7, 1996

[54] **DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF**

[75] Inventors: **Hitoshi Nishiyama**, Neyagawa; **Masaru Ohgaki**, Kobe; **Ryo Yamanishi**, Ibaraki; **Toshihiko Hara**, Miura, all of Japan

[73] Assignee: **Fujisawa Pharmaceutical Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **295,782**

[22] PCT Filed: **Mar. 8, 1993**

[86] PCT No.: **PCT/JP93/00286**

§ 371 Date: **Sep. 12, 1994**

§ 102(e) Date: **Sep. 12, 1994**

[87] PCT Pub. No.: **WO93/19053**

PCT Pub. Date: **Sep. 30, 1993**

[30] **Foreign Application Priority Data**

Mar. 17, 1992 [JP] Japan 4-092070
Oct. 15, 1992 [JP] Japan 4-305093

[51] **Int. Cl.**[6] **A61K 38/12**; A61K 38/15; C07K 11/02

[52] **U.S. Cl.** **530/317**; 530/323

[58] **Field of Search** 514/11, 18; 530/323, 530/317; 930/30

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,116,815 5/1992 Takagi et al. 514/11

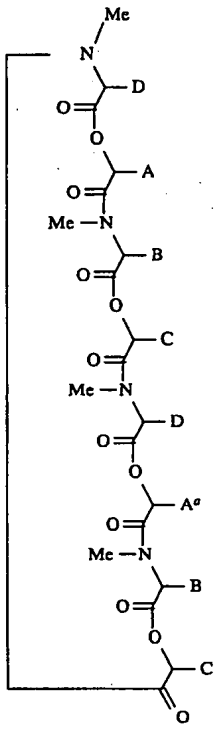
FOREIGN PATENT DOCUMENTS

503538 9/1992 European Pat. Off. .
35796 2/1991 Japan .

Primary Examiner—Jeffrey E. Russel
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

(I)



wherein

A is benzyl group which has suitable substituent(s) or phenyl group which may have suitable substituent(s),

A^a is benzyl group which may have suitable substituent(s) or phenyl group which may have suitable substituent(s),

B and D are each lower alkyl,

C is hydrogen or lower alkyl,

and a pharmaceutically acceptable salt thereof. The compound or a salt thereof of the present invention has excellent parasiticidal activities as an anthelmintic agent for animals and human bodies.

12 Claims, No Drawings

DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF

TECHNICAL FIELD

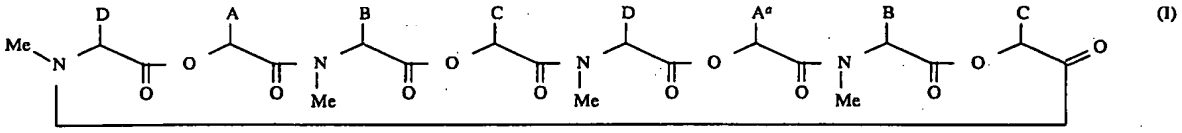
The present invention relates to new depsipeptide derivatives having antiparasitic activity.

BACKGROUND ART

Japanese Kokai Tokkyo Koho 3-35796 discloses depsipeptide derivative prepared by culturing microorganisms.

DISCLOSURE OF INVENTION

The object compound of the present invention, depsipeptide derivatives can be represented by the following general formula (I).



(I)

wherein

A is benzyl group which has suitable substituent(s) or phenyl group which may have suitable substituent(s),

A^a is benzyl group which may have suitable substituent(s) or phenyl group which may have suitable substituent(s),

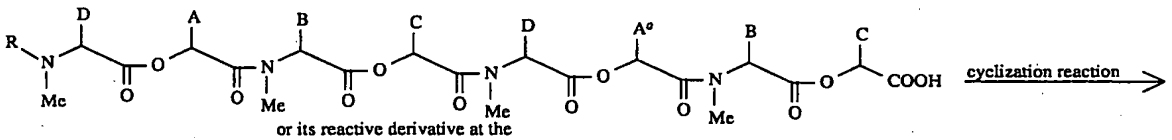
B and D are each lower alkyl,

C is hydrogen or lower alkyl.

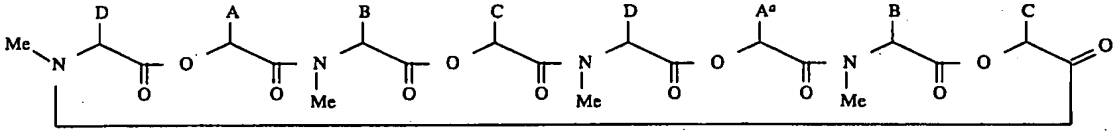
According to the present invention, the object compound of depsipeptide derivatives (I) can be prepared by processes which are illustrated in the following schemes.

It should be indicated that any of D-configured compound, L-configured compound and/or DL-configured compound are in the extent of the present invention; however, for the convenience, only D-configured compounds and L-configured compounds are explained in the process for preparation as follows.

Process 1



or its reactive derivative at the amino or carboxy group or a salt therof

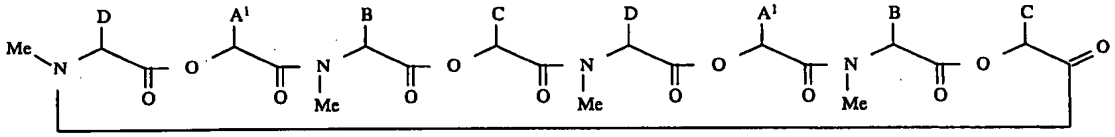


(I)

or a salt thereof

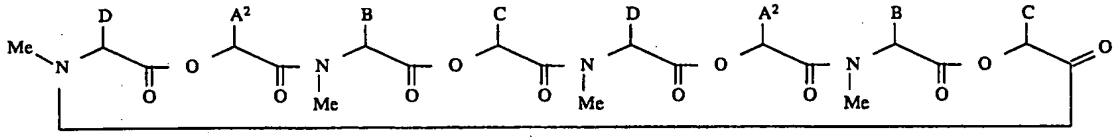
-continued

Process 2



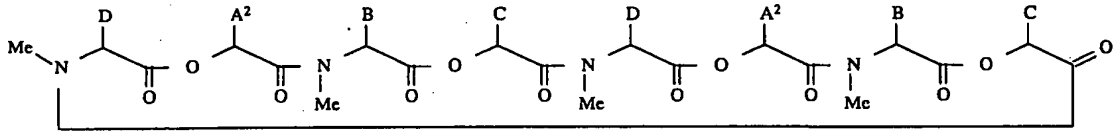
(III)

nitration reaction



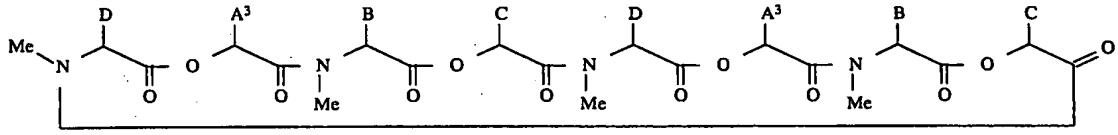
(Ia)

Process 3



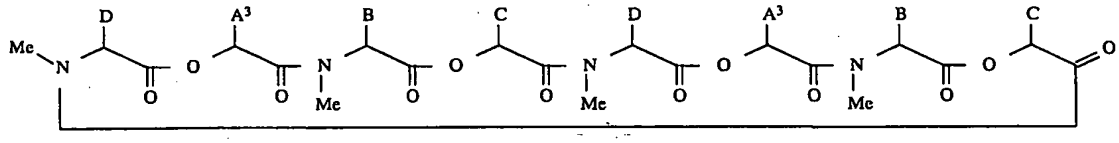
(Ia)

reduction reaction



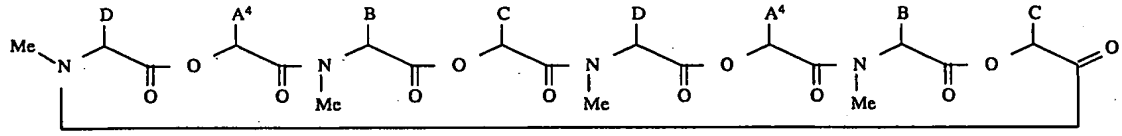
(Ib)

Process 4



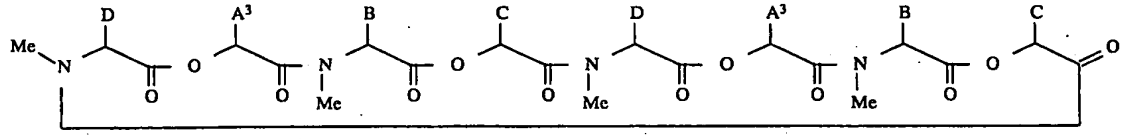
(Ib)

alkylation reaction



(Ic)

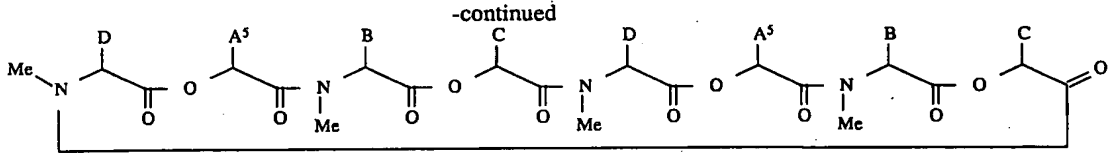
Process 5



(Ib)

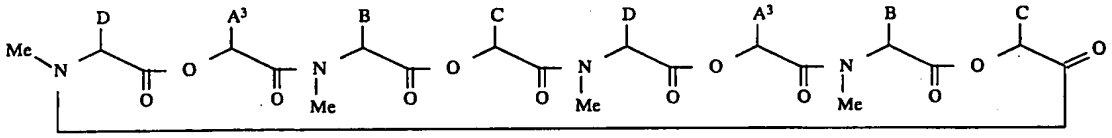
monoalkylation reaction followed by intramolecular alkylation reaction

-continued



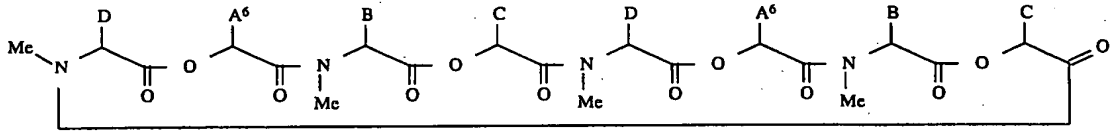
(Id)

Process 6



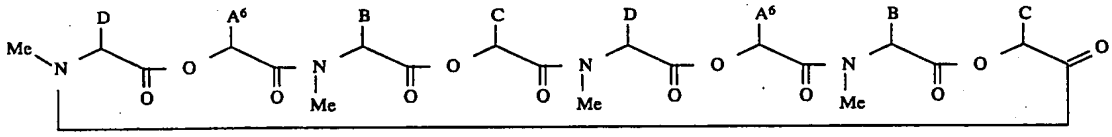
(Ib)

hydroxylation reaction via diazo compound



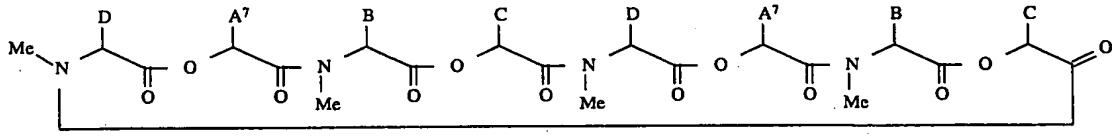
(Ie)

Process 7



(Ic)

alkylation reaction



(If)

wherein

A, A^a, B, C and D are each as defined above,

R is hydrogen or amino protective group,

A^1 is benzyl group which may have lower alkoxy,

A^2 is benzyl group which has nitro, or benzyl group which has nitro and lower alkoxy,

A^3 is benzyl group which has amino, or benzyl group which has amino and lower alkoxy,

A^4 is benzyl group which has mono- or di-lower alkylamino, or benzyl group which has mono- or di-lower alkylamino and lower alkoxy,

A^5 is benzyl group which has cyclic amino, or benzyl group which has cyclic amino and lower alkoxy,

A^6 is benzyl group which has hydroxy, or benzyl group which has hydroxy and lower alkoxy,

A^7 is benzyl group which has lower alkoxy.

Throughout the present specification, the amino acid, peptides, protective groups, condensing agents, etc. are indicated by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be L-configured compounds and residues, and when shown by D- abbreviations, they are meant to be D-configured compounds and residues.

In the present invention, there are employed the following abbreviations.

p-MeOPhLac: 2-hydroxy-3-(4-methoxyphenyl) propionic acid [β-(p-methoxyphenyl)lactic acid]

Man: 2-hydroxyphenylacetic acid [mandelic acid]

p-Me_2NPhLac: 3-(4-dimethylaminophenyl)-2-hydroxypropionic acid [β-(p-dimethylaminophenyl)lactic acid]

p-PipPhLac: 2-hydroxy-3-(4-piperazinophenyl)propionic acid [β-(p-piperazinophenyl)lactic acid]

p-PyrPhLac: 2-hydroxy-3-(4-pyrrolidinophenyl)propionic acid [β-(p-pyrrolidinophenyl)lactic acid

p-NO_2PhLac: 3-(4-nitrophenyl)-2-hydroxypropionic acid [β-(p-nitrophenyl)lactic acid]

p-NH_2PhLac: 3-(4-aminophenyl)-2-hydroxypropionic acid [β-(p-aminophenyl)lactic acid]

p-Et_2NPhLac: 3-(4-diethylaminophenyl)-2-hydroxypropionic acid [β-(p-diethylaminophenyl)lactic acid]

p-Hex_2NPhLac: 3-(4-di-n-hexylaminophenyl)-2-hydroxypropionic acid [β-(p-di-n-hexylaminophenyl)lactic acid]

p-PylPhLac: 2-hydroxy-3-(1H-pyrrol-1-yl-phenyl)propionic acid [β-(p-1H-pyrrol-1-yl)phenyl)lactic acid]

p-OHPhLac: 2-hydroxy-3-(4-hydroxyphenyl)propionic acid [β-(p-hydroxyphenyl)lactic acid]

p-EtOPhLac: 3-(4-ethoxyphenyl)2-hydroxypropionic acid [β-(p-ethoxyphenyl)lactic acid]

p-HexOPhLac: 3-(4-n-hexyloxyphenyl)-2-hydroxypropionic acid [β-(p-n-hexyloxyphenyl)lactic acid]

p-MEPhLac: 2-hydroxy-3-[4-(2-methoxyethoxy)phenyl] propionic acid [β-[p-(2-methoxyethoxy)phenyl]lactic acid]

p-MEEPhLac: 2-hydroxy-3-{4-[2-(2-methoxyethoxy) ethoxy]phenyl}propionic acid [β-{p-[2-(2-methoxyethoxy)ethoxy]phenyl}lactic acid]

o-MeOPhLac: 2-hydroxy-3-(2-methoxyphenyl)propionic acid [β-(o-methoxyphenyl)lactic acid]

m-MeOPhLac: 2-hydroxy-3-(3-methoxyphenyl)propionic acid [β-(m-methoxyphenyl)lactic acid]

3,4-DMOPhLac: 3-(3,4-dimethoxyphenyl)-2-hydroxypropionic acid [β-(3,4-dimethoxyphenyl)lactic acid]

2,4-DMOPhLac: 3-(2,4-dimethoxyphenyl)-2-hydroxypropionic acid [β-(2,4-dimethoxyphenyl)lactic acid]

3,4-MODPhLac: 2-hydroxy-3-(3,4-methylenedioxyphenyl) propionic acid [β-(3,4-methylenedioxyphenyl)lactic acid]

3-MA-4-MOPhLac: 3-(3-dimethylamino-4-methoxyphenyl)-2-hydroxypropionic acid [β-(3-dimethylamino-4-methoxyphenyl)lactic acid]

3,4-DMAPhLac: 3-[(3,4-bis(dimethylamino)phenyl]-2-hydroxyphenyl]propionic acid [β-[3,4-bis(dimethylamino)phenyl]lactic acid]

o-FPhLac: 3-(2-fluorophenyl)-2-hydroxypropionic acid [β-(o-fluorophenyl)lactic acid]

m-FPhLac: 3-(3-fluorophenyl)-2-hydroxypropionic acid [β-(m-fluorophenyl)lactic acid]

p-FPhLac: 3-(4-fluorophenyl)-2-hydroxypropionic acid [β-(p-fluorophenyl)lactic acid]

Glycol: Glycolic acid

PhLac: 2-hydroxy-3-phenylpropionic acid [β-phenyllactic acid]

Lac: 2-hydroxypropionic acid [lactic acid]

p-MorPhLac: 2-hydroxy-3-(4-morpholinophenyl)propionic acid [β-(p-morpholinophenyl)lactic acid]

Suitable salts of the compound (I) are conventional nontoxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkali earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid,etc.); and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom (s), preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable substituent(s) in the term "benzyl group which has substituent(s)", "phenyl group which may have substituent(s)" and "benzyl group which may have substituent(s)" may include hydroxy, lower alkoxy, lower alkoxy lower alkoxy, lower alkoxy lower alkoxy lower alkoxy, halogen, lower alkyl, amino, cyclic amino, nitro, halogen (e.g. fluoro, chloro, bromo, iodo, etc.) and the like. These may have 1 or more than 2 substituents.

Suitable "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s) such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, isopentyloxy, hexyloxy, and the like.

Suitable "lower alkoxy lower alkoxy" may include methoxymethoxy, methoxyethoxy, methoxypropoxy, ethoxyisopropoxy, and the like.

Suitable "lower alkoxy lower alkoxy lower alkoxy" may include methoxymethoxyethoxy, methoxyethoxyethoxy, methoxyethoxypropoxy, ethoxymethoxyisopropoxy, and the like.

Suitable "cyclic amino group" may be aromatic ring or alicyclic compound which have more than 1 nitrogen atom(s) as hetero atom(s), and it containing monocyclic group or condensed polycyclic group which may be saturated or unsaturated. Also, cyclic amino group may further contain hetero atom(s) such as more than 1 or 2 nitrogen atom(s), oxygen atom(s), sulfur atom(s), and the like and still further the cyclic amino group may be spiro ring or bridged cyclic compound. The number of the constructive atom(s) of cyclic amino group are not limited, but for example, monocyclic group have 3 to 8-membered rings and bicyclic have 7 to 11-membered rings.

Example of such cyclic amino group may include saturated or unsaturated monocyclic group which contain one nitrogen atom as hetero atom(s) such as 1-azetidinyl, pyrrolidino, 2-pyrroline-1-yl, 1-pyrrolyl, piperidino, 1,4-dihydropyrizine-1-yl, 1,2,5,6-tetrahydropyrizine-1-yl, homopiperidino and the like, saturated or unsaturated monocyclic group which contain more than two nitrogen atom(s) as hetero atom(s) such as 1-imidazolidinyl, 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 1-tetrazolyl, 1-piperazinyl, 1-homopiperazinyl, 1,2-dihydropyridazine-1-yl, 1,2-dihydropyrimidine-1-yl, perhydropyrimidine-1-yl, 1,4-diazacyclo heptane-1-yl, saturated or unsaturated monocyclic group which contain 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) as hetero atom(s) such as oxazolidine-3-yl, 2,3-dihydroisooxazole-2-yl, morpholino, saturated or unsaturated monocyclic group which contain 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) as hetero atom(s) such as thiazolidine-3-yl, isothiazoline-2-yl, thiomorpholino, condensed polycyclic group such as indole-1-yl, 1,2-dihydrobenzimidazole-1-yl, perhydropyrrolo[1,2-a]pyrazine-2-yl, spirocyclic group such as 2-azaspiro[4,5]decane-2-yl, bridged cyclic heterocyclic group such as 7-azabicyclo[2,2,1]heptane-7-yl, and the like.

Said lower alkoxy, lower alkyl, amino, cyclic amino group and the like may have suitable substutuent(s), such as lower alkylamino which is mono- or di-substituted, lower alkenyl, aralkyl, aryl, hydroxy, hydroxy lower alkyl, nitro, cyano, above mentioned cyclic amino, above mentioned lower alkoxy, lower alkoxy lower alkyl, halogen, halo lower alkyl, amino, protected amino, amino lower alkyl, protected amino lower alky, cyclo lower alkylamino, and the like.

The numbers of these substituent(s) are not limited, preferably 1 to 4, and the substituent(s) may be the same or not the same. Also two of the same or not the same substituent(s) may substitute the same atom(s) on cyclic amino group.

"Mono- or di-lower alkylamino group" may include amino group which has the group of one or two lower alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl, tert-pentyl, etc.), preferably methylamino, ethylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, dibutylamino, etc.

"Lower alkenyl group" may include vinyl, allyl, isopropenyl, and the like. "Aralkyl group" may include benzyl, 1-phenylethyl, and the like.

"Aryl group" may include phenyl, naphthyl, and the like.

"Hydroxy lower alkyl group, alkoxy lower alkyl group, halo lower alkyl group, amino lower alkyl group, protected amino lower alkyl group" means that optional carbon atom(s) of above mentioned lower alkyl has each hydroxy, alkoxy, halogen, amino, protected amino.

"Amino protecting group", may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, pivaloyl, hexanoyl, etc.), mono- (or di- or tri-) halo (lower) alkanoyl group (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.), lower alkoxycarbonyl group, (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc.), carbamoyl group, aroyl group (e.g. benzoyl, toluoyl, naphthoyl, etc.), ar (lower) alkanoyl group (e.g. phenylacetyl, phenylpropionyl, etc.), aryloxycarbonyl group (e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.), aryloxy (lower) alkanoyl group (e.g. phenoxyacetyl, phenoxypropionyl, etc.), arylglyoxyloyl group, (e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.), ar (lower) alkoxycarbonyl group which may have suitable substituent(s), (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.), ar (lower) alkylidene group which are substituted or not substituted (e.g. benzylidene, hydroxybenzylidene etc.), ar (lower)alkyl group such as mono- (or di- or tri-) phenyl (lower) alkyl (e.g. benzyl, phenethyl, benzhydryl, trityl, etc.) and the like.

Above mentioned amino protective group contain the protective group which have the function to temporarily protect amino group which is often used in the field of amino acid and peptide chemistry.

Suitable "benzyl group which has lower alkoxy" may include lower alkoxy substituted benzyl such as 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 2,3,4-trimethoxybenzyl, 2-ethoxybenzyl, 4-hexyloxybenzyl, etc.

Suitable "benzyl group which has halogen" may include halogen substituted benzyl such as 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2-bromobenzyl, 2-bromo-4-chlorobenzyl, etc.

Suitable "benzyl group which has lower alkyl" may include lower alkyl substituted benzyl such as 4-methylbenzyl, 4-ethylbenzyl, 4-propylbenzyl, 4-isopropylbenzyl, 4-butylbenzyl, 4-isobutylbenzyl, 4-tert-butylbenzyl, 4-pentylbenzyl, 4-hexylbenzyl, 2,3-dimethylbenzyl, 2,6-dimethylbenzyl, 3,4-dimethylbenzyl, 2,4,6-trimethylbenzyl, etc.

Suitable example of phenyl group which have such substituent(s) may include lower alkoxy substituted phenyl group (e.g. 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2-ethoxyphenyl, 4-hexyloxyphenyl, etc.), halogen substituted phenyl (e.g. 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 2-bromophenyl, 2-bromo-4-chlorophenyl, 4-fluorophenyl, 2,4-difluorophenyl etc.), hydroxy substituted phenyl (e.g. 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, etc.), lower alkoxy- and hydroxy-substituted phenyl (e.g. 2-(hydroxymethoxy) phenyl, etc.).

Suitable example of benzyl group which have such substituent(s) may include lower alkoxy substituted benzyl (e.g. 4-methoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 2,3,4-trimethoxybenzyl, 2-ethoxybenzyl, 4-hexyloxybenzyl, etc.), halogen substituted benzyl (e.g. 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2bromobenzyl, 2-bromo-4-chlorobenzyl, etc.), hydroxy substituted benzyl (e.g. 2-hydroxybenzyl, 3-hydroxybenzyl, 4-hydroxybenzyl, etc.), lower alkoxy and hydroxy substituted benzyl (e.g. 2-(hydroxymethoxy) benzyl, etc.)

More preferable example of "cyclic amino group which may have substituent(s)" may include pyrrolidino, morpholino, 1-piperazino, 4-methylpiperazino, piperidino and the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by subjecting the compound (II) or its reactive derivative at the amino group or carboxy group or a salt thereof to cyclization reaction.

The starting compound (II), its reactive derivative or a salt thereof is new and such compounds can be prepared by the methods described in Preparation mentioned below or in substantially the same manner.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as a aliphatic carboxylic acid [e.g. acetic acid, propionic acid, burytic acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride, and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used. The reaction is usually carried out in the usual method which is used in cyclization reaction, under heating or in the presence of a conventional condensing agent. When R in the compound (II) is amino protective group, the elimination of the amino protective group is carried out previous to ring cyclization reaction.

Suitable condensing agent may include carbodiimide or a salt thereof [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or hydrochloride thereof, diphenyl phosphoryl azide, diethyl phosphorocyanidate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, etc.]; N,N'-carbonyldiimidazole, N,N'-carbonylbis-(2-methylimidazole); keteneimine compound(e.g. pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylen; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thionyl chloride; oxalyl chloride; combining triphenylphosphine, and carbon tetrachloride or siazen carboxylate; 2-ethyl-7-hydroxybenzisoxazolium salt;

2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 1-hydroxybenzotriazol; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction in the presence of conventional condensing agent may be carried out in an organic solvent such as dichloromethane, methanol, ethanol, propanol, acetonitrile, pyridine, N,N-diethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, benzene, toluene, xylene, etc. or any other solvent mixture which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. Further, ring cyclization reaction under heating can be carried out to heat under boiling point in the solvent which is used in an organic solvent as above.

Process 2

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (III) or a salt thereof to nitration reaction.

The starting compounds (III) contain known compounds (Japanese Kokai Tokkyo Koho No. 3-35796) and novel compounds. The novel compounds can be prepared by the procedures described in Preparations and Examples mentioned later or in substantially the same manner.

This reaction is carried out by reacting the compound (III) or a salt thereof with nitration agent (e.g. nitric acid, etc.).

The reaction can usually be carried out in a conventional solvent such as dichloromethane which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

This reaction can be carried out in substantially the same manner as Example 7 mentioned later.

Process 3

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to the reduction reaction.

This reaction can be carried out in a conventional manner for reducing: nitro to amino, and it may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.]. palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The object compound (Ic) or a salt thereof can be prepared by subjecting the isolated or not isolated the compound (Ib) or a salt thereof, which is obtained by the Process 3, to alkylation reaction. This reaction can be carried out by combining aldehyde and reduction agent or alkylhalide and base. Suitable reduction agents are metallic hydride complex compound, [e.g. sodium borohydride, sodium cyanoborohydride, potassium borohydride, bis(2-methoxyethoxy) aluminium hydride, etc.], a combination of hydrogen, formic acid, or ammonium formate, and palladium catalysts [e.g. palladium on carbon, palladium hydroxide on carbon, palladium black, etc.].

Suitable base may include an inorganic base such as sodium bicarbonate, potassium carbonate, etc., or an organic base such as pyridine, triethylamine, etc. The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction. The reaction which is combined by aldehyde and reduction agents can be carried out in substantially the same manner as Preparation 23 or Example 8 mentioned later, and the reaction which is combined by an alkyl halide and a base can be carried out in substantially the same manner as Preparation 41 mentioned later.

The reaction which is combined by the compound containing two aldehydes and reduction agents can be carried out in substantially the same manner as Example 31 mentioned later.

Process 5

The object compound (Id) or a salt thereof can be prepared by subjecting the isolated or not isolated compound (Ib) or a salt thereof, which is obtained by the Process 3, to mono alkylation reaction followed by intramolecular alkylation reaction. The reaction can be carried out by combining a compound, which has two aldehydes in the molecule, and reduction agents or by combining a compound, which has two halogens and a base.

Process 6

The object compound (Ie) or a salt thereof can be prepared by subjecting the isolated or not isolated object compound (Ib) or a salt thereof, which is obtained by the Process 3, to hydroxylation reaction by diazotization reaction followed by decomposition of diazonium salt. This reaction can be carried out by reacting the compound (Ib) or a salt thereof with sodium nitrite in the presence of an inorganic or an organic acid and decomposing a growing diazonium salt in water or an organic acid under the room temperature to heating, carrying out hydrolysis if necessary. It is possible to prepare the compound (Ie) or a salt thereof by transforming the amino group of the compound (Ib) or a salt thereof into a hydroxyl group. Suitable acid may include an inorganic acid [e.g. sulfuric acid, hydrochloric acid, borofluoric acid, etc.], and an organic acid [e.g. acetic acid, trifluoroacetic acid, etc.].

Process 7

The object compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt, which is obtained by the Process 6, thereof to alkylation reaction. This reaction can be prepared by combining a alkylhalide and a base.

The reaction can be carried out substantially in the same manner as the later mentioned Example 15 and Example 16.

Suitable base may include an inorganic base [e.g. sodium bicarbonate, potassium carbonate, etc. and an organic base [e.g. pyridine, triethylamine, etc.].

The compound or its salt of the present invention has excellent parasiticidal activities as an anthelmintic agent for animals and human bodies. It is effective to nematodes which are infected particularly to the domestic animals, domestic fowls or pets such as pigs, sheep, goats, cattle, horses, dogs, cats, and chickens.

Haemonchus genus, Trichostrongylus genus, Ostertagia genus, Nematodirus genus, Cooperia genus, Ascaris genus, Bunostomum genus, Oesophagostomum genus, Chabertia genus, Trichuris genus, Strongylus genus, Trichonema genus, Dictyocaulus genus, Capillaria genus, Heterakis genus, Toxocara genus, Ascaridia genus, Oxyuris genus, Ancylostoma genus, Uncinaria genus, Toxascaris genus, Parascaris genus, Nippostrongylus genus, Metastrongylus genus, Hyostrongylus genus, Strongyloides genus, Cyathostomum genus.

The parasiticidal activities are pointed out in some kind of Nematodirus genus, Cooperia genus, and Oesophagostomum genus which attack the intestinal tract, however, just Haemonchus genus and Ostertagia genus are parasitic on the stomach, and parasites of Dictyocaulus genus are found in lungs.

The parasites of Filariidae or Setariidae activities are found in heart and blood vessels, hypodermis, or lymphatic vessel or any other organisms or organs.

It is also effective to parasites which infect human beings. The most common parasites in the alimentary canal of human beings are as follows:

Ancylostoma genus, Necator genus, Ascaris genus, Strongyloides genus, Tichinell genus, Capillaria genus, Trichuris genus, and Enterobius genus.

It is also active for other medically important parasites, which is found in the blood or other organisms or organs out side of the alimentary canal, such as Wuchereria genus, Brugia genus, Onchocerca genus and Loa genus in Filariidae, as well as parasites such as Dracunlus genus in Dracunculidae. It is also active for parasites such as Strongyloides genus and Trichinella genus in the intestinal tract in a particular conditioned parasitism out side of intestinal tract.

Test

Test 1

(1) Test Compounds

The compounds which are illustrated in Example 1, Example 3, Example 4, Example 5, Example 10, Example 17, Example 23, Example 24, Example 25, and Example 29.

(2) Test

The effect of parasiticides was examined with the rats which was infected by nematodes which are parasitic on rats, *Nippostrongylus brasilienses.*

Wistar strain rats (female 6 weeks old, 120–130 g weight) were sacrificed by infecting them and giving them subcutaneous injections of 3000 infective larvae per rat.

Test compound of 50 mg was dissolved in 0.25 ml dimethylsulfoxide, 0.5% methylcellulose solution was added, and liquid volume was adjusted to be prescribed volume of 100, 10, 5, 2.5, 1.25, 1.0, 0.63, 0.32 mg/kg to utilize. After they were infected, on each 7th, 8th, and 9th day, the test compound was administered orally with above concentration. On the 11th day, the rat was dissected and the numbers of parasites in the small intestines were measured.

The given measurement was based to calculate the reduction rate from the percentage of the numbers of the parasites of unadministered rats (control). The result of it is shown in the

Test 2

The reduction rate was calculated in a similar manner as Test 1 except when the test compound was subcutaneously administered to the rats instead of oral administration as in Test 1. The result of that is shown in the Table 2.

Test 3

For 1 rat, the 5000 infective larvae of *Strongyloides venezuelensis* were infected percutaneously to one group (2 rats) of 8 weeks old Mongolian gerbils. On the 10th day after they were infected, the suspended test compound was orally administered once with the amount of established administration. The effect was judged according to the amount of the eggs in the feces or the numbers of worms in the intestinal tract. The measurement of the numbers of the eggs were taken from O ring method, and the numbers of the eggs (EPG) in 1 g of feces were counted on the day before, on the day, and on the 1st, 2nd, 3rd, and 4th day after the administration. The numbers of the parasites were measured by dissecting Mongolian gerbils the 4th day after the administration (on the 14th day after infection). The method of measurement was followed by releasing the parasites, which live in the small intestines, into saline solution over night, and the released parasites were set to be as numbers of worms recovered.

The result (the mean number of each group) is shown in the Table 3.

Test Results

TABLE 1

Test Compounds	Minimum Amount of Administration indicated by more than 95% of Reduction Rate
PF1022 (Japanese Patent Application 3 - 35796)	10 mg/kg
Example - 1	2.5 mg/kg
Example - 3	1.25 mg/kg
Example - 4	2.5 mg/kg
Example - 5	0.63 mg/kg
Example - 10	2.5 mg/kg
Example - 17	2.5 mg/kg
Example - 23	5 mg/kg
Example - 24	5 mg/kg
Example - 25	5 mg/kg
Example - 29	5 mg/kg

TABLE 2

Test Compounds	Minimum Amount of Administration indicated by more than 95% of Reduction Rate
PF1022 (Japanese Patent Application 3 - 35796)	>100 mg/kg
Example - 1	10 mg/kg
Example - 3	5 mg/kg
Example - 5	1.25 mg/kg
Example - 12	50 mg/kg

TABLE 3

Test		Change in Numbers of Parasites' Number of Eggs in Feces (EPG/100)						Numbers of the Worms
Compounds	Dose	−2	0*	1	2	3	4	recovered
Unadministered control	—	574	1240	1725	2343	1533	1505	3005
PF1022	20 mg/kg	332	1615	581	1563	935	1005	3088
Example-5	5 mg/kg	455	1890	701	0	0	0	0
Example-5	2.5 mg/kg	838	1665	452	0	0	0	0
Example-5	1.25 mg/kg	551	2800	536	0	0	30	8

*stands for the starting day of administration.

When the compound of the present invention are used for animals and human being as an anthelmintic agent, it can be administered orally as a liquid drink. The liquid drink is usually suspended agent such as bentonite, and wetting agent, or other excipients with non-toxic solution, or solution made of water, suspension, or dispersed solution, and generally it comprises liquid drinks or antifoaming agent. The prescription of a liquid drink contains generally activated compound for 0.01–0.5 weight %, preferably 0.0–0.1 weight %. When it is preferably administered orally as a dried solid single dose, capsules, pills, or tablets, which comprise the desired amount of activated compounds are usually used. These forms of dosage are prepared by homogeneous admixtures of diluent, filler, disintegrator and/or excipient agents such as dextrine, lactose, talc, magnesium stearate, vegetable rubber, etc.

The usage of such single dose prescription can be varied broadly by kind of hosts, or kind of parasites, or weight of hosts which are to be treated and referring to the weight and containing quantity of anthelmintics.

When it is administered in animal feed, it is used as to disperse homogeneously, or as top dressing, or in the form of pellet. To achieve preferable effect of antiparasites, the activated compound of 0.0001–2% is usually contained in feed.

The dosage which was dissolved or dispersed in liquid carrier excipients can be administered to animals parenterally by giving them injections in the anterior stomach, muscle, tachea, or under the skin. The activated compound is mixed with suitable vegetable oil such as peanut oil or cottonseed oil for parenteral administration. These prescriptions generally contain the activated compound of 0.05–50 weight %. It can also be administered locally by mixing in a suitable carrier such as dimethylsulfoxide or hydrocarbon solvent. The prepared solvents can be used directly on the exterior of animals by sprays or direct injections.

The most suitable usage amount of the activated compound to achieve the most effective result depends on the kind of animals, which are to be treated, and type of parasital infection and its stage. It can be achieved by oral administration of the activated compound 0.01–100 mg, preferably 0.5–50.0 mg, per kg of the treated animal. Such dosage amount is given in a relatively short term of 1–5 days at once or separately.

The Preparations and Examples of the present invention are shown in the following.

Preparation 1

Boc-Tyr (Me)-OH (5.1 g), was dissolved in 4N-hydrogen chloride in dioxane (87.5 ml) and stirred under ice-cooling for 2 hours. After dioxane was evaporated in vacuo, the residue was dissolved in 6N-hydrochloric acid aqueous solution (45 ml) and at 0° C., sodium nitrite (1.9 g) was added by portions. After stirring for 4 hours, the reaction solution was extracted with ether (100 ml×3). After washing ether layer by saturated brine, the extract was dried over calcium chloride and the solvent was evaporated in vacuo. To the residue, benzene (30 ml), benzyl alcohol (3.4 ml) and p-toluenesulfonic acid mono hydrate (0.22 g) were added and heated under reflux for 3 hours by using Dean Stark apparatus. After cooling down to the room temperature, the crude product, which was gained by evaporating the solvent, was purified by silica gel chromatography (eluting with ethyl acetate: hexane=1:10, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate (1.79 g).

NMR ($CDCl_3$, δ): 3.12 (dd,1H), 3.29 (dd,1H), 3.78 (s,3H), 4.44 (t, 1H), 5.07–5.25 (m,2H), 6.77–7.36 (m,9H).

Preparation 2

To a solution of Boc-MeLeu-OH (1.37 g) in methanol (30 ml) and water (10 ml) was added 20% aqueous cesium carbonate solution to be pH7.0. After the solvent was evaporated in vacuo, azeotroped three times by toluene (10 ml). The residue was dissolved in dimethylformamide (20 ml), under ice-cooling, benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate (1.79) was added and stirred at room temperature for 24 hours. The reaction solution was poured into water (150 ml), extracted with ether (100 ml×3), washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:8, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-OBzl (1.59 g).

NMR ($CDCl_3$,δ): 0.90 (d,6H), 1.41 (s) and 1.49 (s) (9H), 1.40–1.58 (m, 3H), 2.62–2.67 (m,3H), 3.06–3.15 (m,2H), 3.77 (s,3H), 4.68–4.80 (m) and, 4.97–5.29 (m) (4H), 6.78 (d,2H), 7.06 (d,2H), 7.26–7.36 (m,5H).

Preparation 3

To a solution of Boc-MeLeu-D-p-MeOPhLac-OBzl (1.36 g) in methanol (15 ml) was added 10% palladium on carbon (0.4 g), and hydrogenated at atmospheric pressure of hydrogen gas for 45 minutes at ambient temperature. The catalyst

was filtered off, the solvent was evaporated to give Boc-MeLeu-D-p-MeOPhLac-OH (1.08 g).

NMR ($CDCl_3$,δ): 0.89–0.95 (m,6H), 1.44 (s,9H), 1.44–1.79 (m,3H), 2.66–2.82 (m,3H), 3.01–3.20 (m,2H), 3.79 (s,3H), 4.40–4.75 (m,1H),5.15–5.38 (m,1H), 6.82 (d,2H), 7.14 (d,2H).

Preparation 4

Boc-MeLeu-D-Lac-OBzl (1.04 g) was dissolved in 4N-hydrogen chloride in dioxane (12.5 ml), under ice-cooling stirred for 3 hours. After the solvent was evaporated in vacuo, azeotroped twice by toluene (10 ml) to give H-MeLeu-D-Lac-OBzl.HCl (1g).

NMR ($CDCl_3$, δ): 0.94–1.00 (m,6H), 1.59 (d,3H), 1.78–2.13 (m,3H), 2.62–2.75 (m,3H), 3.78–3.85 (m,1H), 5.09–5.29 (m,3H), 7.25–7.43 (m,5H), 9.80–10.00 (m,1H), 10.30–10.55 (m,1H).

Preparation 5

To the mixture of Boc-MeLeu-D-pMeOPhLac-OH (1g), H-MeLeu-D-Lac-OBzl.HCl (1 g) in dichloromethane (20 ml) and triethylamine (15 ml) was added bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.98 g), and was stirred for 13 hours. The water (50 ml) was added to the mixture and it was extracted with ethyl acetate (50 ml×3). After it was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (1.59 g).

NMR ($CDCl_3$,δ): 0.80–0.99 (m,12H), 1.42–1.80 (m,18H),2.66–3.04 (m,8H), 3.78 (s,3H), 4.64–5.43 (m,6H), 6.81 (d,2H), 7.12–7.39 (m,7H).

Preparation 6

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl was used instead of Boc-MeLeu-D-p-MeOPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.67 g) was obtained according to a similar manner to that of

Preparation 3.

NMR ($CDCl_3$,δ): 0.82–0.94 (m,12H), 1.46 (s,9H), 1.40–1.80 (m,9H), 2.67–3.29 (m,8H), 3.77 (s,3H), 4.83–5.71 (m,4H), 6.80 (d,2H), 7.15 (d,2H).

Preparation 7

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.75 g) was dissolved in 4N-hydrogen chloride in ethyl acetate (5.25 ml), and it was stirred under ice-cooling for three hours. After the solvent was evaporated in vacuo, it was azeotroped twice by toluene (10 ml) to give H-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl.HCl (0.74 g).

NMR ($CDCl_3$,δ): 0.77–1.00 (m,12H), 1.21–1.98 (m,9H), 2.61–3.10 (m,8H),3.77 (s,3H), 3.62–3.82 (m,1H), 5.04–5.55 (m,6H), 6.83 (d,2H). 7.12–7.34 (m,7H), 9.30–9.50 (m,1H), 10.40–10.59 (m,1H).

Preparation 8

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.67 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl.HCl (0.74 g) was used instead of H-MeLeu-D-Lac-OBzl.HCl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.80–0.99 (m,24H), 1.10–1.70 (m,2.7H), 2.65–3.10 (m,16H), 3.77 (s,6H), 4.61–5.49 (m,10H), 6.78–6.85 (m,4H), 7,12–7.40 (m,9H).

Preparation 9

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.92 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-pMeOPhLac-MeLeu-D-Lac-OH (0.89 g) was obtained according to a similar manner to that of Preparation 3.

NMR ($CDCl_3$,δ): 0.79–0.99 (m,24H), 1.10–1.80 (m,2.7H), 2.65–3.10 (m,16H),3.77 (s,6H), 4.60–5.65 (m,8H), 6.78–6.90 (m,4H),7.13–7.25 (m,4H).

Preparation 10

To a solution of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.89 g) and pentafluorophenol (0.14 g) in dichloromethane (10 ml) were added under ice-cooling, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride (0.22 g), and stirred for 3 hours. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-pMeOPhLac-MeLeu-D-Lac-OC_6F_5 (0.8 g).

NMR ($CDCl_3$,δ): 0.80–0.99 (m,24H), 1.10–1.80 (m,2.7H), 2.65–3.18 (m,16H),3.77 (s,6H), 4.60–5.55 (m,8H), 6.78–6.90 (m,4H), 7.10–7.22 (m,4H).

Preparation 11

To a solution of H-D-Man-OH (1 g) and triethylamine (0.92 ml) in ethyl acetate (50 ml) was added phenacyl bromide (1.31 g) under ice-cooling. After the mixture was stirred for 48 hours at room temperature, the reaction mixture was poured into water and was extracted with ethyl acetate (50 ml×3). After the extract was dried over anhydrous magnesium sulfate, it was concentrated in vacuo to give H-D-Man-OPac (1.7 g).

NMR ($CDCl_3$,δ): 5.30 (d,1H), 5.41 (s,1H), 5.47 (d,1H), 7.31–7.88 (m,10H).

Preparation 12

To a solution of Boc-MeLeu-OH (1.54 g), and H-D-Man-OPac (1.7 g) in methylene chloride (50 ml) were added dimethylaminopyridine (77mg) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.hydrochloride (1.32 g) under ice-cooling, The mixture was stirred for 3 hours successively. After methylene chloride was evaporated in vacuo, ethyl acetate (200 ml) was added, and washed with water, the solution was dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-Man-OPac (3 g).

NMR ($CDCl_3$,δ): 0.91–0.97 (m,6H), 1.39 (s) and 1.43 (s) (9H),1.40–1.86 (m,3H), 2.85 (s) and 2.88 (s) (3H), 4.80–4.88 (m) and 5.04–5.12 (m) (1H), 5.29 (d,1H), 5.40 (d,1H),6.11 (s) and 6.15 (s) (1H), 7.40–7.86 (m,10H).

Preparation 13

To 90% aqueous acetic acid (30 ml) of Boc-MeLeu-D-Man-OPac (3 g) was added zinc powder (3 g) and stirred for 1 hour at room temperature. After filtering the zinc residue, the solvent was evaporated in vacuo. Ethyl acetate (200 ml) was added to the residue, and washed with 10% aqueous citric acid, water, and saturated brine. After drying over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of methylene chloride, ethanol and acetic acid (20:1:0.1, v/v). The frac-

tions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-Man-OH (2.22 g).

NMR ($CDCl_3$,δ): 0.91–0.97 (m,6H), 1.28 (s) and 1.44 (s) (9H),1.40–1.80 (m,3H), 2.86 (s,3H), 4.80–4.98 (m,1H), 5.95 (s,1H), 7.39–7.50 (m,5H).

Preparation 14

Trichloroethyl (S)-2-chloropropionate (4.8 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-Lac-OTce (7.98 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.93–0.98 (m,6H), 1.47 (s,9H), 1.59 (d,3H), 1.50–1.78 (m,3H), 2.81 (s) and 2.84 (s) (3H), 4.64–5.05 (m,3H), 5.19 (q,1H).

Preparation 15

Boc-MeLeu-D-Lac-OTce (2.7 g) was used instead of Boc-MeLeu-D-Lac-OBzl. Except above matter, H-MeLeu-D-Lac-OTce.HCl (2.45 g) was obtained according to a similar manner to that of Preparation 4.

NMR ($CDCl_3$,δ): 0.95–1.03 (m,6H), 1.68 (d,3H), 1.80–2.16 (m,3H), 2.74–2.80 (m,3H), 3.80–3.99 (m,1H), 4.67 (d,1H), 4.96 (d,1H), 5.32 (q,1H), 9.80–10.10 (m,1H), 10.30–10.60 (m,1H).

Preparation 16

Boc-MeLeu-D-Man-OH (2.22 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-Lac-OTce-.HCl (2.4 g) was used instead of H-MeLeu-D-Lac-OBzl-.HCl. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (3.33 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.77–0.99 (m,12H), 1.35 (s,9H), 1.26–1.84 (m,9H), 2.79–2.98 (m,6H), 4.53–5.55 (m,5H), 6.15–6.24 (m,1H), 7.39–7.46 (m,5H).

Preparation 17

Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.5 g) was used instead of Boc-MeLeu-D-Man-OPac. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OH (1.46 g) was obtained according to a similar manner to that of Preparation 13.

NMR ($CDCl_3$,δ): 0.79–0.99 (m,12H), 1.37 (s,9H), 1.20–1.83 (m,9H), 2.79–2.96 (m,6H), 4.53–5.40 (m,3H), 6.14–6.26 (m,1H), 7.39–7.44 (m,5H).

Preparation 18

Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.5 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl. Except above matter, H-MeLeu-D-Man-MeLeu-D-Lac-OTce.HCl (1.3 g) was obtained according to a similar manner to that of Preparation 7.

NMR ($CDCl_3$,δ): 0.78–0.98 (m,12H), 1.30–2.24 (m,9H), 2.78–2.97 (m.6H), 3.79–3.99 (m,1H), 4.52–5.56 (m,4H), 6.27–6.31 (m,1H),7.40–7.52 (m,5H), 9.52–9.90 (m,1H), 10.10–10.42 (m,1H).

Preparation 19

Boc-MeLeu-D-Man-MeLeu-D-Lac-OH (1.4 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-Man-MeLeu-D-Lac-OTce.HCl (1.3 g) was used instead of H-MeLeu-D-Lac-OBzl.HCl. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.7 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.76–1.18 (m,24H), 1.21–1.98 (m,2.7H), 2.79–3.10 (m,12H), 4.52–5.59 (m,8H), 6.13–6.25 (m,2H), 7.15–7.55 (m,10H).

Preparation 20

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OTce was used instead of Boc-MeLeu-D Man-OPac. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OH (1.07 g) was obtained according to a similar manner to that of Preparation 13.

NMR ($CDCl_3$,δ): 0.70–1.10 (m,24H), 1.35 (s,9H), 1.25–1.98 (m,18H), 2.78–3.09 (m,12H), 4.20–5.59 (m,6H), 6.10–6.37 (m,2H), 7.26–7.59 (m,10H).

Preparation 21

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OH was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OC_6F_5 (0.96 g) was obtained according to a similar manner to that of Preparation 10.

NMR ($CDCl_3$,δ): 0.72–1.00 (m,24H), 1.10–1.95 (m,2.7H), 2.77–3.09 (m,12H), 4.40–5.68 (m,6H), 6.12–6.24 (m,2H), 7.22–7.58 (m,10H).

Preparation 22

To a solution of ethyl (R)-2-acetoxy-3-(4-nitrophenyl) propionate (5.62 g) in ethanol (50 ml) were added concentrated hydrochloric acid (2.5 ml) and 10% palladium on carbon (0.6 g). The mixture was hydrogenated under atmospheric pressure of hydrogen gas for 3 hours at room temperature. The catalyst was filtered off and the solvent was evaporated in vacuo. To the residue was added 0.05N hydrochloric acid (200 ml) and washed with ether (100 ml×2). Saturated aqueous sodium hydrogencarbonate was added to water layer until pH10, and extracted with ether (100 ml×4). After the ether layer was washed with saturated brine, it was dried over anhydrous magnesium sulfate and evaporated in vacuo. To the residue, benzene (40 ml), benzylalcohol (21 ml) and p-toluenesulfonic acid-mono hydrate (4.76 g) were added, and the mixture was heated under reflux for 4 hours. After ice-cooling down to room temperature, the solvent was evaporated in vacuo. To the residue was added water (200 ml) and washed with ether (100 ml×2). Saturated aqueous sodium hydrogencarbonate was added to water layer until pH10, extracted with ether (100 ml×4). After the ether layer was washed with saturated brine, it was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo to give benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (2.84 g).

NMR ($CDCl_3$,δ) 2.85 (dd,1H),2.6–3.6 (m,3H),3.00 (dd, 1H),4.38 (dd,1H), 5.15 (s,2H),6.53 (d,2H),6.90 (d,2H), 7.25–7.4 (m,5H)

IR (neat): 1740 cm^{-1}

Preparation 23

To a solution of benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (0.26 g) in acetic acid (6 ml) was added paraformaldehyde (0.3 g), and further sodium cyanoborohydride (0.3 g) was added gradually, and stirred for 3 hours. To the solution of sodium bicarbonate (25 ml) and ice (25 g) was added reaction mixture gradually and was extracted with ethyl acetate (50 ml×2). After washing the ethyl acetate layer with saturated brine, it was dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-3(4-dimethylaminophenyl)-2-hydroxypropionate (0.22 g). NMR ($CDCl_3$,δ) 2.64 (d,1H),2.91 (s,6H), 2.90 (dd,1H),3.04 (dd,1H),4.43 (ddd,1H), 5.18 (s,2H),6.63 (d,2H),7.01 (d,2H),7.35 (bs,5H)

IR (neat): 1733, 1612 cm^{-1}

Preparation 24

To a solution of Boc-MeLeu-OH (1.27 g), H-D-p-Me_2NPhLac-OBzl (1.47 g) in methylene chloride (20 ml)

were added under ice-cooling, dimethylaminopyridine (0.15 g), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride (1.01 g), and stirred for 15 hours successively. The solvent was evaporated in vacuo. The water (50 ml) was added to residue and extracted with ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to give Boc-MeLeu-D-p-Me_2NPhLac-OBzl (1.69 g).

NMR ($CDCl_3$,δ) 0.90 (d,6H),1.4–1.65 (m,12H),2.63 (s) and 2.68 (s) (3H),2.93 (s,6H),3.05–3.15 (m,6H),4.65–4.80 (m) and 4.95–5.20 (m) (4H),6.62 (d,2H),7.03 (d,2H),7.1–7.2 (m,5H)

IR (KBr): 1747,1730,1693,1675, cm^{-1}

Preparation 25

To a solution of Boc-MeLeu-D-p-Me_2NPhLac-OBzl (1.67 g) in methanol (30 ml) and tetrahydrofuran (5 ml) was added 10% palladium on carbon (0.3 g), and hydrogenation was done in hydrogen gas under atmospheric pressure for 1 and 0.5 hour. After catalyst was filtrated, the solvent was evaporated in vacuo to give Boc-MeLeu-D-p-Me_2NPhLac-OH (1.44 g).

IR (KBr): 1741,1694 cm^{-1}

Preparation 26

To a mixture of Boc-MeLeu-D-p-Me_2NPhLac-OH (1.44 g) in triethylamine (1.92 ml) and dichloromethane (15 ml) was added under ice-cooling, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.30 g) and stirred successively for 15 and ½ hours. The solvent was evaporated in vacuo, and water (50 ml) was added and extracted with ethyl acetate (50 ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (1.55 g).

NMR ($CDCl_3$,δ) 0.8–1.0 (m,12H),1.4–1.7 (m,18H), 2.7–3.1 (m,8H),2.90 (s,6H),5.65–6.5 (m,6H),6.65 (d,2H), 7.08 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1663 cm^{-1}

Preparation 27

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.77 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (637 mg) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1694,1663 cm^{-1}

Preparation 28

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (765 mg) was dissolved in 4N hydrogen chloride in ethyl acetate (5 ml), and stirred for 2 hours at room temperature. After the solvent was evaporated in vacuo, it was azeotroped twice with toluene (10 ml) to obtain 2HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (783 mg)

IR (KBr): 1744,1647 cm^{-1}

Preparation 29

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.78 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.88 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.75–1.0 (m,24H),1.2–1.8 (m,2.7H), 2.65–3.1 (m,16H), 2.91 (s,12H),4.65–5.5 (m,10H),6.6–6.75 (m,4H),7.0-7.15 (m,4H),7.3–7.7 (m,5H)

IR (KBr): 1740,1694,1662 cm^{-1}

FAB-MS: 1243 $[M+H]^+$

Preparation 30

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.87 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1735,1695,1662 cm^{-1}

Preparation 31

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.81 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.826 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1743,1646 cm^{-1}

Preparation 32

The suspended solution of benzyl R)-3-(4-aminophenyl)-2-hydroxypropionate (0.27 g), bis(2-chloroethyl)ether (0.12 ml), potassium carbonate (0.28 g), and sodium iodide (0.075 g) in dimethylformamide (1 ml) were heated at 70°–90° C. for 7 hours. After cooling it down to room temperature, water (50 ml) was added and extracted with ether (25 ml×3). After the ether layer was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane, ethyl acetate and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-morpholinophenyl)propionate (0.14 g)

NMR ($CDCl_3$,δ) 2.66 (d,1H),2.91 (dd,1H),3.05 (dd,1H), 3.0–3.15 (m,4H), 3.8–3.95 (m,4H),4.45 (ddd,1H),5.18 (s,2H),6.79 (d,2H),7.05 (d,2H),7.3–7.4 (m,5H)

IR (neat): 1734 cm^{-1}

EI-MS: 341 $[M]^+$

Preparation 33

H-D-p-MorPhLac-OBzl (0.90 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.36 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ) 0.9 (d,6H),1.4–1.65 (m,12H),2.63 (s) and 2.66 (s) (3H), 3.05–3.2 (m,6H),3.85–3.95 (m,4H), 4.7–4.8 (m) and 4.95–5.25 (m) (4H),6.80 (d,2H),7.07 (d,2H),7.1–7.2 (m,5H)

IR (KBr): 1740,1695 cm^{-1}

Preparation 34

Boc-MeLeu-D-p-MorPhLac-OBzl (1.35 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-OH (1.08 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1742,1695 cm^{-1}

Preparation 35

Boc-MeLeu-D-p-MorPhLac-OH (1.08 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above

matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.49 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ) 0.85–0.95 (m,12H),1.4–1.7 (m,18H), 2.78 (s),2.81 (s) and 2.88 (s) (6H),3.0–3.1 (m,2H),3.1–3.15 (m,4H),3.85–3.9 (m,4H),4.65–4.75 (m) and 4.9–5.5 (m) (6H),6.82 (d,2H),7.13 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1662 cm^{-1}

Preparation 36

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.64 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1741,1694,1664 cm^{-1}

Preparation 37

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.73 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1648 cm^{-1}

Preparation 38

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.73 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.08 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.8–1.05 (m,24H),1.15–1.8 (m,2.7H), 2.65–3.2 (m,24H), 3.8–3.95 (m,8H),4.65–4.75 (m) and 4.9–5.5 (m) (10H),6.75–6.9 (m,4H), 7.05–7.2 (m,4H), 7.3–7.4 (m,5H)

IR (KBr): 1738,1694,1663 cm^{-1}

FAB-MS: 1227 $[M+H]^+$

Preparation 39

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.07 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.96 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1694,1663 cm^{-1}

Preparation 40

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (1.02 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

Preparation 41

The suspended solution of benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (1.53 g), 1,4-dibromobutane (0.61 ml), potassium carbonate (2.07 g) and sodium iodide (0.37 g) in dimethylformamide (5 ml) were stirred at room temperature for 71 hours. To the solution was added water (50 ml) and extracted with ether (50 ml, 25 ml×2). After the ether layer was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane and ethyl acetate (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-pyrrolidinophenyl) propionate (1.35 g).

NMR ($CDCl_3$,δ) 1.95–2.05 (m,4H),2.61 (d,1H),2.90 (dd, 1H),3.03 (dd,1H), 3.2–3.3 (m,4H),4.43 (ddd,1H),5.18 (s,2H),6.45 (d,2H),6.99 (d,2H),7.3–7.4 (m,5H)

IR (neat): 1732 cm^{-1}

Preparation 42

H-D-p-PyrPhLac-OBzl (1.34 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-OBzl (1.79 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ) 0.92 (d,6H),1.4–1.65 (m,12H),1.95–2.1 (m,4H),2.47 (s) and 2.52 (s) (3H),3.0–3.15 (m,2H),3.2–3.35 (m,4H),4.7–4.8 (m) and 5.0–5.25 (m) (4H),6.46 (d,2H),7.02 (d,2H), 7.1–7.2 (m,5H)

IR (KBr): 1750,1740,1692,1672 cm^{-1}

Preparation 43

Boc-MeLeu-D-p-PyrPhLac-OBzl (1.78 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-OH (1.44 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695 cm^{-1}

Preparation 44

Boc-MeLeu-D-p-PyrPhLac-OH (1.44 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (1.53 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.8–0.95 (m,12H),1.4–1.7 (m,18H), 1.95–2.05 (m,4H), 2.7–3.05 (m,8H),3.2–3.3 (m,4H), 5.65–5.75 (m) and 5.9–6.5 (m) (6H), 6.47 (d,2H),7.06 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1741,1695,1662 cm^{-1}

Preparation 45

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.65 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 46

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.77 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1743,1646 cm^{-1}

Preparation 47

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.82 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.75–1.05 (m,24H),1.1–1.75 (m,2.7H), 1.9–2.1 (m,8H), 2.65–3.1 (m,28H),3.1–3.3 (m,8H),4.6–4.8 (m) and 4.9–5.5 (m) (10H), 6.35–6.55 (m,4H),7.0–7.2 (m,4H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1664 cm^{-1}

FAB-MS: 1295 $[M+H]^+$

Preparation 48

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.80 g) was used instead of

Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.74 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 49

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1647 cm^{-1}

Preparation 50

1,4-dibromobutane (0.56 ml) was used instead of 1,5-dibromopentane. Except above matter, benzyl (R)-2-hydroxy-3-(4-piperidinophenyl) propionate (1.05 g). was obtained according to a similar manner to that of Preparation 41.

NMR ($CDCl_3$,δ): 1.50–1.80 (m,6H),2.65 (d,1H),2.90 (dd, 1H),3.05 (dd,1H), 3.05–3.2 (m,4H),4.44 (ddd,1H),5.17 (s,2H),6.82 (d,2H),7.01 (d,2H),7.3–7.4 (m,5H)

IR (neat): **1720**cm^{-1}

Preparation 51

H-D-p-PipPhLac-OBzl (0.79 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.71 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.90 (d,6H),1.4–1.8 (m,18H),2.62 (s) and 2.66 (s) (3H),3.0–3.15 (m,6H),4.65–4.75 (m) and 4.95–5.25 (m) (4H),6.82 (d,2H), 7.03 (d,2H),7.2–7.35 (m,5H)

IR (KBr): 1741,1695 cm^{-1}

Preparation 52

Boc-MeLeu-D-p-PipPhLac-OBzl (1.68 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-OH (1.38 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1694 cm^{-1}

Preparation 53

Boc-MeLeu-D-p-PipPhLac-OH (1.38 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (2.01 g) was obtained according to a similar manner to that of Preparation 26

NMR ($CDCl_3$,δ): 0.8–0.95 (m,12H),1.3–1.75 (m,24H), 2.7–3.15 (m,12H), 4.65–4.75 (m) and 4.9–6.4 (m,6H),6.84 (d,2H),7.09 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 54

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (0.99 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (0.84 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1665 cm^{-1}

Preparation 55

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (0.98 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1649 cm^{-1}

Preparation 56

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (0.84 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.06 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.18 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.0 (m,24H),1.05–1.8 (m,39H), 2.65–3.2 (m,24H), 4.65–4.75 (m) and 4.9–5.5 (m) (10H), 6.8–6.9 (m,4H),7.0–7.15 (m,4H),7.3–7.4 (m,5H)

IR (KBr): 1738,1694,1663 cm^{-1}

FAB-MS: 1323 $[M+H]^+$

Preparation 57

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.17 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.11 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1693,1662 cm^{-1}

Preparation 58

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.10 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter 3HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.24 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1742,1652 cm^{-1}

Preparation 59

Under nitrogen atmosphere, to a suspended solution of anhydrous tetrahydrofuran (1 ml) and metal magnesium (0.3 g) was added dropwise a solution of 4-(2-methoxyethoxy) bromobenzene (2.9 g) in anhydrous tetrahydrofuran (15 ml) at room temperature. After the dropping, the solution was heated under reflux at 100° C. for 15 minutes, and then the residue was cooled down to −10° C., added to cuprous bromide.dimethylsulfide complex (1.29 g), and stirred for 30 minutes at −5° C.–3° C. Further, it was cooled down to −60° C., and the solution (5 ml) of benzyl (R)-2,3-epoxypropionate (0.74 g) in anhydrous tetrahydrofuran was added dropwise for 30 minutes and stirred for 1 and ½ hour successively. To the solution were added saturated aqueous ammonium chloride (10 ml), and water (50 ml), and was extracted with ethyl acetate (100 ml×2). After washing the ethyl acetate layer with saturated brine, the solution was dried over sodium sulfate and evaporated in vacuo. The solvent was evaporated in vacuo, the resultant crude product was purified by silica get chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-4-(2-methoxyethoxy) phenyl lactic acid (1.09 g).

NMR ($CDCl_3$,δ): 2.92 (dd,1H),3.06 (dd,1H),3.47 (s,3H), 3.74 (t,2H),4.08 (t,2H),4.45 (dd,1H),5.17 (s,2H),6.8 (d,2H), 7.0 (d,2H),7.29–7.48 (m,5H)

Preparation 60

H-D-p-MEPhLac-OBzl (0.92 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.15 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.90 (d,6H),1.4–1.65 (m,12H),2.6–2.7 (m,3H),3.01–3.12 (m,2H),3.45 (s,3H),3.67–3.78 (m,2H), 4.02–4.12 (m,2H),4.62–5.22 (m,4H),6.77–6.86 (m,2H), 7.02–7.12 (m,2H),7.22–7.4 (m,5H)

FAB-MS: 458 $[M-Boc+H]^+$

Preparation 61

Boc-MeLeu-D-p-MEPhLac-OBzl (1.5 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except

above matter Boc-MeLeu-D-p-MEPhLac-OH (1.29 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.03 (m,6H),1.38–1.8 (m,12H), 2.7–2.9 (m,3H), 3.0–3.3 (m,2H),3.45 (s,3H),3.65–3.78 (m,2H),4.05–4.17 (m,2H),4.4–4.51 (m) and 4.63–4.77 (m) (1H),5.2–5.38 (m,1H),6.85 (d,2H),7.13 (d,2H)

Preparation 62

Boc-MeLeu-D-p-MEPhLac-OH (1.29 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.87 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–0.95 (m,12H),1.4–1.7 (m,18H), 2.79–2.97 (m,6H), 3.01–3.09 (m,2H),3.45 (s,3H),3.64–3.79 (m,2H),4.02–4.17 (m,2H), 4.6–4.8 (m) and 4.9–5.43 (m) (6H),6.85 (d,2H),7.07–7.19 (m,2H),7.3–7.42 (m,5H)

FAB-MS: 657 $[M\text{-}Boc+H]^+$

Preparation 63

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.85 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-p-MEPhLac-MeLeu-D-Lac-OH (0.67 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.99 (m,12H),1.4–1.7 (m,18H), 2.76–2.95 (m,6H), 3.0–3.19 (m,2H),3.45 (s,3H),3.74—3.8 (m,2H),4.04–4.18 (m,2H),4.65–4.9 (m) and 5.12–5.39 (m) (4H),6.83 (d,2H),7.15 (d,2H)

Preparation 64

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.86g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter HCl.H-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.86 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.79–1.03 (m,12H),1.21–2.18 (m,9H), 2.56–2.72 (m,3H), 2.83–2.99 (m,3H),2.99–3.12 (m,2H), 3.45 (s,3H),3.63–3.8 (m,3H),4.03–4.17 (m,2H),5.03–5.58 (m,5H),6.86 (d,2H),7.07–7.43 (m,7H)

Preparation 65

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (0.66 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, HCl.H-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.84 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.24 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.0 (m,24H),1.15–1.79 (m,2.7H), 2.7–3.17 (m,16H), 3.45 (s,6H),3.66–3.78 (m,4H),4.02–4.14 (m,4H),4.6–4.78 (m) and 4.9–5.5 (m) (10H),6.78–6.95 (m,4H),7.03–7.18 (m,4H),7.3–7.42 (m,5H)

FAB-MS: 1205 $[M\text{-}Boc+H]^+$

Preparation 66

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.22 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (1.03 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.77–1.02 (m,24H),1.18–1.8 (m,2.7H), 2.7–3.09 (m,16H), 3.45 (s,6H),3.65–3.8 (m,4H),3.98–4.17 (m,4H),4.58–5.77 (m,5H), 6.84 (d,4H),7.14 (d,4H)

Preparation 67

Under nitrogen atmosphere, at −15° C., to dichloromethane solution of (R)-isopropylidene glycerol (2 g) and triethylamine (5.05 ml) was added dropwise dichloromethane solution of trifluoromethanesulfonic anhydride (3.05 ml). After stirring for half an hour successively, dichloromethane was added and the mixture was washed with water, saturated aqueous sodium bicarbonate, saturated brine and dried over anhydrous sodium sulfate and filtrated with silica gel. The solvent was evaporated in vacuo and azeotroped by toluene to gain the crude product of triflate. To tetrahydrofuran solution of magnesium (0.61 g) was added dropwise tetrahydrofuran solution of 2-bromoanisole (2.82 ml), and for half an hour it was heated under reflux. Under ice-cooling, the copper bromide dimethylsulfide complex (0.99 g) was then added. Further tetrahydrofuran solution of the above crude product of triflate was added dropwise and stirred for 2 hours successively, aqueous ammonium chloride was added, and was extracted with ethyl acetate. The extract was dried magnesium over sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of ethyl acetate and hexane (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.25 g).

NMR ($CDCl_3$,δ): 1.35 (s,3H),1.44 (s,3H),2.81 (dd,1H), 3.02 (dd,1H),3.66 (dd,1H),3.81 (s,3H),3.88 (dd,1H),4.37 (dt, 1H),6.79–6.93 (m,2H),7.13–7.25 (m,2H)

Preparation 68

(R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.2 g) was dissolved in ethanol (20 ml) and to 6N-aqueous hydrochloric acid solution was added and stirred for 2 hours at room temperature. After evaporating ethanol in vacuo, water was added and extracted with ethyl acetate. After washing with aqueous saturated sodium bicarbonate solution, it was dried over sodium sulfate and evaporated in vacuo to give (R)-3-(2- methoxyphenyl)propane-1,2-diol (1.62 g).

NMR ($CDCl_3$,δ): 2.75–2.93 (m,2H),3.40–4.00 (m,3H), 3.85 (s,3H),6.82–6.97 (m,2H),7.12–7.28 (m,2H)

Preparation 69

Under ice-cooling, to a solution of (R)-3-(2-methoxyphenyl)propane-1,2-diol (1.62 g) and imidazole (0.92 g) in dimethylformamide was added t-butyldimethylsilyl chloride (1.36 g), and stirred for 15minutes successively. The reaction solution was poured into water, extracted with ethyl acetate, and dried over sodium sulfate. After the solvent was evaporated in vacuo, the gained crude product was purified by silica gel column chromatography, and it was eluted with a mixed solvent of hexane and ethyl acetate (7:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol (2.22 g).

NMR ($CDCl_3$,δ): 0.063 (s,6H),0.91 (s,9H),2.59 (d,1H), 2.78–2.84 (m,2H), 3.45–3.68 (m,2H),3.88 (s,3H),3.89–3.97 (m,1H),6.83–6.94 (m,2H),7.16–7.26 (m,2)

Preparation 70

Under ice-cooling, to a dichloromethane solution of (R)1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol (2.2 g) were added diisopropylethylamine (2.59 ml) and methoxymethylchloride (0.85 ml) and stirred at room temperature for 18 hours. After evaporating dichloromethane in vacuo, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the resultant crude product was purified by silica gel column chromatography, and it was eluted with a mixed solvent of hexane and ethyl acetate (6:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl)propane (2.22 g).

NMR ($CDCl_3$,δ): 0.04 (s,6H),0.89 (s,9H),2.68 (dd,1H), 2.91 (dd,1H),3.15 (s,3H),3.63 (d,2H),3.79 (s,3H),3.82–3.99 (m,1H),4.52 (d,1H),4.67 (d,1H), 6.80–6.91 (m,2H), 7.11–7.26 (m,2H)

Preparation 71

Under ice-cooling, to a tetrahydrofuran solution of (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl) propane (2.2 g) was added a solution of n tetrabutylammonium fluoride (1 mol/l, 6.46 ml) in tetrahydrofuran and stirred for 2 hours successively. After tetrahydrofuran was evaporated in vacuo, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo, the gained crude product was purified by silica gel column chromatography, and eluted with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol (1.51 g).

NMR ($CDCl_3$,δ): 2.85 (d,2H),3.36 (s,3H),3.41–3.70 (m,2H),3.83 (s,3H), 3.82–3.98 (m,1H),4.62 (d,1H),4.68 (d,1H),6.83–6.92 (m,2H),7.12–7.26 (m,2H)

Preparation 72

To dimethylformamide solution (17.5 ml) of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol (1.5 g) was added pyridinium dichromate (8.73 g) and stirred for 15 hours at room temperature. To the reaction solution was added silica gel and ethyl acetate. The mixture was filtered through silica gel. The solvent was evaporated in vacuo, ethyl acetate-benzene (1:1) was added, washed with water and dried over magnesium sulfate. After the solvent was evaporated in vacuo, tetrahydrofuran (6 ml), 6N-aqueous hydrochloric acid (6 ml) was added and stirred for 2 hours at 50° C. After tetrahydrofuran was evaporated in vacuo, water was added, extracted with ethyl acetate, washed with water, and dried over magnesium sulfate. After the solvent was evaporated in vacuo, dimethylformamide, potassium carbonate (0.7 g) was added and under ice-cooling, benzyl bromide was added dropwise. After the mixture was stirred for 1 and ½ hour, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane and ethyl acetate (3:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(2-methoxyphenyl)propionate (1.02 g).

NMR ($CDCl_3$,δ): 2.92 (d,1H),3.03 (dd,1H),3.18 (dd,1H), 3.83 (s,3H),4.46–4.58 (m,1H),5.11 (d,1H),5.19 (d,1H), 6.83–6.91 (m,2H),7.18–7.38 (m,7H)

El-MS:286 $[M]^+$

Preparation 73

H-D-o-MeOPhLac-OBzl (1 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-OBzl (1.73 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.88 (d,6H),1.18–1.65 (m,12H), 2.58–2.78 (m,3H),2.98–3.38 (m,2H),3.79 (s,3H),4.66–5.00 (m,1H),5.08–5.18 (m,2H),5.20–5.40 (m,1H),6.76–6.89 (m,2H),7.07–7.40 (m,7H)

Preparation 74

Boc-MeLeu-D-o-MeOPhLac-OBzl (1.7 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-OH (1.54 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.95 (m,6H),1.20–1.62 (m,12H), 2.69–2.74 (m,3H), 3.02 (dd,1H),3.31–3.43 (m,1H),3.82 (s,3H),4.51–4.72 (m,1H),5.25–5.43 (m,1H),6.80–6.92 (m,2H),7.11–7.26 (m,2H)

Preparation 75

Boc-MeLeu-D-o-MeOPhLac-OH (1.5 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (2.09 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.99 (m,12H),1.20–1.80 (m,18H), 2.70–3.34 (m, 8H),3.84 (s) and 3.79 (s) (3H),4.59–5.58 (m,6H),6.81–6.92 (m,2H),7.13–7.35

Preparation 76

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (0.98 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.01 (m,12H),1.10–1.78 (m,18H), 2.69–3.21 (m,8H), 3.86 (s,3H),4.62–5.92 (m,4H),6.81–6.92 (m,2H),7.12–7.26 (m,2H)

Preparation 77

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-o MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.68–1.01 (m,12H),1.10–1.98 (m,9H), 2.56–3.40 (m,8H), 3.67–3.82 (m,1H),3.84 (s,3H),4.95–5.72 (m,5H),6.81–6.93 (m,2H), 7.15–7.36 (m,7H)

Preparation 78

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (0.98 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1.26 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.79–1.00 (m,24H),1.19–1.82 (m,2.7H),2.72–3.19 (m,16H), 3.79–3.92 (m,6H),4.61–5.62 (m,10H),6.77–6.93 (m,4H),7.17–7.38 (m,9H)

Preparation 79

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1.25g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (1.24 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.00 (m,24H),1.15–1.82 (m,2H), 2.62–3.22 (m,16H), 3.85 (s,6H),4.42–5.90 (m,8H), 6.80–6.92 (m,4H),0.15–7.26 (m,4H)

Preparation 80

3-bromoanisole (2.82 ml) was used instead of 2-bromoanisole. Except above matter, (R)-4-(3-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.25 g) was obtained according to a similar manner to that of Preparation 67.

NMR ($CDCl_3$,δ): 1.36 (s,3H),1.44 (s,3H),2.73 (dd,1H), 3.00 (dd,1H),3.61 (dd,1H),3.79 (s,3H),3.97 (dd,1H),4.32 (dt,1H),6.76–6.82 (m,3H),7.17–7.23 (m,1H)

Preparation 81

(R)-4-(3-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (1.3 g) was used instead of (R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane. Except above matter, (R)-3-(3-methoxyphenyl)propane-1,2-diol (1 g) was obtained according to a similar manner to that of Preparation 68.

NMR ($CDCl_3$,δ): 1.93 (t,1H),2.06 (d,1H),2.67–2.82 (m,2H),3.47–3.79 (m,2H),3.81 (s,3H),3.90–4.02 (m,1H), 6.77–6.84 (m,3H),7.20–7.28 (m,1H)

Preparation 82

(R)-3-(3-methoxyphenyl)propane-1,2-diol (0.99 g) was used instead of (R)-3-(2-methoxyphenyl)propane-1,2-diol. Except above matter, (12)-1-t-butyldimethylsiloxy-3-(3-methoxyphenyl)-2-propanol (1.4 g) was obtained according to a similar manner to that of Preparation 69.

NMR ($CDCl_3$,δ): 0.065 (s,6H),0.91 (s,9H),2.40 (d,1H), 2.75 (d,2H),3.45 (dd,1H),3.61 (dd,1H),3.79 (s,3H), 3.85–4.00 (m,1H),6.75–6.83 (m,3H),7.17–7.26 (m,1H)

Preparation 83

(R)-1-t-butyldimethylsiloxy-3-(3-methoxyphenyl)-2-propanol (1.4 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol. Except above matter (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy 3-(3-methoxyphenyl)propane (1.5 g) was obtained according to a similar manner to that of Preparation 70.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.91 (s,9H),2.71 (dd,1H), 2.89 (dd,1H),3.16 (s,3H),3.53–3.68 (m,2H),3.80 (s,3H), 3.79–3.90 (m,1H),4.51 (d,1H),4.68 (d,1H),6.72–6.85 (m,3H),7.11–7.20 (m,1H)

Preparation 84

(R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(3-methoxyphenyl)propane (1.5 g) was used instead of (R)-1t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl)propane. Except above matter, (R)-2-methoxymethoxy-3-(3-methoxyphenyl)-1-propanol (0.93 g) was obtained according to a similar manner to that of Preparation 71.

NMR ($CDCl_3$,δ): 2.69–2.92 (m,2H),3.35 (s,3H), 3.45–3.68 (m,2H),3.79 (s,3H),3.70–3.86 (m,1H),4.57 (d,1H),4.68 (d,1H),6.73–6.83 (m,3H),7.16–7.26 (m,1H)

Preparation 85

(R)-2-methoxymethoxy-3-(3-methoxyphenyl)-1-propanol (0.93 g) was used instead of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol. Except above matter, benzyl (R)-2-hydroxy-3-(3-methoxyphenyl)propionate (0.61 g) was obtained according to a similar manner to that of Preparation 72.

NMR ($CDCl_3$,δ): 2.72 (d,1H),2.95 (dd,1H),3.10 (dd,1H), 3.77 (s,3H),4.41–4.55 (m,1H),5.18 (s,2H),6.71–6.80 (m,3H),7.13–7.39 (m,6H)

Preparation 86

H-D-m-MeOPhLac-OBzl (0.6 g) was used instead of HD-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.26–1.57 (m,12H), 2.62–2–2.75 (m,3H),3.02–3.22 (m,2H),3.76 (s,3H), 4.62–5.30 (m,4H),6.73–6.79 (m,3H),7.14–7.34 (m,6H)

Preparation 87

Boc-MeLeu-D-m-MeOPhLac-OBzl (lg) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-OH (0.93 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–0.98 (m,6H),1.30–1.80 (m,12H), 2.64–2.80 (m,3H), 3.03–3.32 (m,2H),3.79 (s,3H),4.42–5.40 (m,2H),6.76–6.84 (m,3H), 7.16–7.26 (m,1H)

Preparation 88

Boc-MeLeu-D-m-MeOPhLac-OH (0.93 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (1.28 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.99 (m,12H),1.20–1.75 (m,18H), 2.75–2.92 (m,6H), 3.00–3.20 (m,2H),3.78 (s,3H),4.62–5.50 (m,6H),6.76–6.84 (m,3H), 7.17–7.39 (m,6H)

Preparation 89

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.6 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.98 (m,12H),1.10–1.75 (m,18H), 2.73–3.22 (m,8m), 3.78 (s,3H),4.60–5.85 (m,4H),6.75–6.85 (m,3H),7.18–7.25 (m,1H)

Preparation 90

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.61 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.6 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.62–1.00 (m,12H),1.10–1.98 (m,9H), 2.56–3.10 (m,8H), 3.70–3.82 (m,1H),3.79 (s,3H),5.02–5.59 (m,5H),6.75–6.90 (m,3H), 7.15–7.40 (m,6H)

Preparation 91

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.6 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH and HCl.H-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.6 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.82 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.70–1.02 (m,24H),1.20–1.79 (m,2.7H),2.70–3.19 (m,16), 3.78 (s,6H),5.01–5.60 (m,10H), 6.70–6.92 (m,6H),7.18–7.34 (m,7H)

Preparation 92

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.82 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.79 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.75–1.00 (m,24H),1.10–1.80 (m,2.7H),2.60–3.19 (m,16H), 3.78 (s,6H),4.58–5.78 (m,8H),6.71–6.90 (m,6H),7.12–7.35 (m,2H)

Preparation 93

1-bromo-3,4-dimethoxybenzene (1.83 g) was used instead of 4-(2-methoxyethoxy) bromobenzene. Except above matter, benzyl (R)-2-hydroxy-3-(3,4-dimethoxyphenyl)propionate (0.23 g) was obtained according to a similar manner to that of

Preparation 59.

NMR ($CDCl_3$,δ): 2.71 (d,1H),2.93 (dd,1H),3.08 (dd,1H), 3.79 (s,3H),3.85 (s,3H),4.42–4.55 (m,1H),5.19 (s,2H), 6.65–6.76 (m,3H),7.26–7.40 (m,5H)

Preparation 94

H-D-3,4-DMOPhLac-OBzl (0.23 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-OBzl (0.34 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.39–1.62 (m,12H), 2.62–2.73 (m,3H),3.0–3.19 (m,2H),3.82 (s,3H),3.85 (s,3H), 4.62–5.32 (m,4H),6.65–6.80 (m,3H), 7.20–7.40 (m,5H)

Preparation 95

Boc-MeLeu-D-3,4-DMOPhLac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-OH (0.3 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.85–0.96 (m,6H),1.42 (s,9H), 1.22–1.69 (m,3H),2.73–2.82 (m,3H),2.95–3.22 (m,2H),3.85 (s,3H),3.87 (s,3H),4.38–4.70 (m,1H), 5.21–5.39 (m,1H), 6.72–6.83 (m,3H)

Preparation 96

Boc-MeLeu-D-3,4-DMOPhLac-OH (0.3 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.41 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.98 (m,12H),1.35–1.69 (m,18H), 2.77–3.15 (m,8H), 3.85 (s,3H),3.87 (s,3H),4.62–5.48 (m,6H),6.72–6.80 (m,3H),7.26–7.39 (m,5H)

Preparation 97

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.2 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.00 (m,12H),1.24–1.80 (m,18H), 2.74–3.16 (m,8H), 3.85 (s,3H),3.87 (s,3H),4.59–5.78 (m,4H),6.77 (s,3H)

Preparation 98

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.18 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.78–0.98 (m,12H),1.20–2.00 (m,9H), 2.62–3.15 (m,8H), 3.69–3.82 (m,1H),3.85 (s,3H),3.87 (s,3H),5.02–5.60 (m,5H),6.74–6.82 (m,3H),7.22–7.38 (m,5H)

Preparation 99

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.18 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.27 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.70–1.00 (m,24H),1.20–1.79 (m,2.7H),2.72–3.18 (m,16H), 3.84 (s,6H),3.86 (s,6H), 4.62–5.48 (m,10H),6.72–6.83 (m,6H),7.21– 7.40 (m,5H)

Preparation 100

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.26 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.26 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.76–1.02 (m,24H),1.32–1.75 (m,2.7H),2.72–3.20 (m,16H), 3.85 (s,6H),3.87 (s,6H), 4.60–5.70 (m,8H),6.72–6.80 (m,6H)

Preparation 101

1-bromo-2,4-dimethoxybenzene (2.93 g) was used instead of 4-(2-methoxyethoxy)bromobenzene. Except above matter, benzyl (R)-2-hydroxy-3-(2,4-dimethoxyphenyl)propionate (1.28 g) was obtained according to a similar manner to that of

Preparation 59.

NMR ($CDCl_3$,δ): 2.87 (d,1H),2.96 (dd,1H),3.10 (dd,1H), 3.76 (s,3H),3.78 (s,3H),4.43–4.53 (m,1H),5.12 (d,1H),5.19 (d,1H),6.36–6.43 (m,2H),6.99 (d,1H),7.21–7.40 (m,5H)

Preparation 102

H-D-2,4-DMOPhLac-OBzl (1.27 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-OBzl (2.16 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.36–1.60 (m,12H), 2.61–2.70 (m,3H),2.92–3.29 (m,2H),3.76 (s,3H),3.77 (s,3H),4.60–5.35 (m,4H),6.31–16.40 (m, 2H),6.97 (d,1H), 7.19–7.40 (m,5H)

Preparation 103

Boc-MeLeu-D-2,4-DMOPhLac-OBzl (2.15 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-OH (1.61 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–0.93 (m,6H),1.38–1.62 (m,12H), 2.73 (brs,3H), 2.91–3.39 (m,2H),3.78 (s,6H),4.58–4.70 (m,1H),5.20–5.39 (m,1H),6.37–6.44 (m,2H),7.03 (d,1H)

Preparation 104

Boc-MeLeu-D-2,4-DMOPhLac-OH (1.6 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (2.2 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.05 (m,12H),1.32–1.65 (m,18H), 2.75–3.15 (m,8H), 3.78 (s,3H),3.81 (s,3H),4.60–5.60 (m,6H),6.30–6.46 (m,2H),7.00–7.09 (m,1H),7.25–7.40 (m,5H)

Preparation 105

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.15–1.78 (m,18H), 2.70–3.12 (m,8H), 3.78 (s,3H),3.83 (s,3H),4.60–5.87 (m,4H),6.30–6.42 (m,2H),7.04 (d,1H)

Preparation 106

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.98 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.69–1.02 (m,12H),1.20–2.00 (m,9H), 2.58–3.20 (m,8H), 3.70–3.80 (m,1H),3.78 (s,3H),3.81 (s,3H),5.00–5.71 (m,5H),6.37–6.46 (m,2H),7.07 (d,1H), 7.20–7.42 (m,5H)

Preparation 107

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.98 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.48 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.82–1.00 (m,24H),1.15–1.80 (m,2.7H),2.75–3.21 (m,16H), 3.72–3.84 (m,12H),4.60–5.60 (m,10H),6.31–6.49 (m,4H),7.00–7.17 (m,2H),7.21–7.40 (m,5H)

Preparation 108

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.45 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1.49 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δd): 0.80–1.02 (m,24H),1.20–1.90 (m,2.7H),2.71–3.22 (m,16H), 3.81 (s) and 3.78 (s) (12H), 4.60–5.80 (m,8H),6.33–6.46 (m,4H), 7.01–7.15 (m,2H)

Preparation 109

1-bromo-3,4-methylenedioxybenzene (2.05 ml) was used instead of 2-bromoanisole. Except above matter, (R)-4-(3,4-methylenedioxybenzyl)-2,2-dimethyl-1,3-dioxolane (1.64 g) was obtained according to a similar manner to that of Preparation 67.

NMR ($CDCl_3$,δ): 1.35 (s,3H),1.43 (s,3H),2.69 (dd,1H), 2.91 (dd,1H),3.62 (dd,1H),3.97 (dd,1H),4.27 (dt,1H),5.93 (s,2H),6.58–6.78 (m,3H)

Preparation 110

(R)-2,2-dimethyl-5-(3,4-methylenedioxybenzyl)-1,3-dioxolane (1.63 g) was used instead of (R)-2,2-dimethyl-5-(2-methoxybenzyl)-1,3-dioxolane. Except above matter, (R)-3-(3,4-methylenedioxyphenyl)propane-1,2-diol (1.37 g) was obtained according to a similar manner to that of Preparation 68.

NMR ($CDCl_3$,δ): 2.63 (dd,1H),2.72 (dd,1H),3.48 (dd, 1H),3.67 (dd,1H), 3.80–3.96 (m,1H),5.92 (s,2H),6.58–6.78 (m,3H)

Preparation 111

(R)-3-(3,4-methylenedioxyphenyl)-propane-1,2-diol (1.25 g) was used instead of (R)-3-(2-methoxyphenyl)propane-1,2-diol. Except above matter, (R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-propanol (1.77 g) was obtained according to a similar manner to that of Preparation 69.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.91 (s,9H),2.69 (d,2H), 3.46 (dd,1H),3.61 (dd,1H),3.79–3.85 (m,1H),5.93 (s,2H), 6.63–6.77 (m,3H)

Preparation 112

(R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-propanol (1.77 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol. Except above matter, (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)propane (1.79 g) was obtained according to a similar manner to that of Preparation 70.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.90 (s,9H),2.65 (dd,1H), 2.83 (dd,1H),3.20 (s,3H),3.52–3.62 (m,2H),3.71–3.83 (m,1H),4.52 (d,1H),4.68 (d,1H),5.92 (s,2H),6.64–6.75 (m,3H)

Preparation 113

(R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-methoxymethoxypropane (1.77 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-methoxymethoxypropane. Except above matter, (R)-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)-1-propanol (1.17 g) was obtained according to a similar manner to that of Preparation 71.

NMR ($CDCl_3$,δ): 2.69 (dd,1H),2.79 (dd,1H),3.37 (s,3H), 3.49 (dd,1H),3.63 (dd,1H),3.71–3.82 (m,1H),4.58 (d,1H), 4.68 (d,1H),5.93 (s,2H),6.62–6.78 (m,3H)

Preparation 114

(R)-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)-1-propanol (0.92 g) was used instead of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol. Except above matter, benzyl (R)-2-hydroxy-3-(3,4-methylenedioxyphenyl)propionate (0.33 g) was obtained according to a similar manner to that of Preparation 72.

NMR ($CDCl_3$,δ): 2.72 (d,1H),2.88 (dd,1H),3.04 (dd,1H), 4.38–4.55 (m,1H), 5.19 (s,2H),5.92 (s,2H),6.53–6.70 (m,3H),7.25–7.40 (m,5H)

Preparation 115

H-D-3,4-MODPhLac-OBzl (0.5 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-OBzl (0.74 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.91 (d,6H),1.38–1.70 (m,12H), 2.62–2.83 (m,3H),2.98–3.20 (m,2H),4.55–5.26 (m,4H),5.92 (s,2H),6.52–6.75 (m,3H),7.21–7.40 (m,5H)

Preparation 116

Boc-MeLeu-D-3,4-MODPhLac-OBzl (0.73 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-OH (0.63 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,6H),1.20–1.80 (m,12H), 2.63–2.93 (m,3H), 2.95–3.25 (m,2H),4.43–4.90 (m,1H), 5.09–5.36 (m,1H),5.93 (s,2H),6.60–6.82 (m,3H)

Preparation 117

Boc-MeLeu-D-3,4-MODPhLac-OH (0.63 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.85 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.20–1.82 (m,18H), 2.69–3.06 (m,8H), 4.60–5.60 (m,6H),5.88–5.97 (m,2H), 6.68–6.80 (m,3H),7.26–7.40 (m,5H)

Preparation 118

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.42 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MOD-PhLac-MeLeu-D-Lac-OH (0.393)was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.20–1.80 (m,18H), 2.65–3.20 (m,8H), 4.60–5.80 (m,4H),5.93 (s,2H),6.62–6.78 (m,3H)

Preparation 119

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.43 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBz. Except above matter, HCl.H-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.4 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ):0.78–1.05 (m,12H),1.20–2.40 (m,9H), 2.60–3.25 (m,8H), 3.60–3.90 (m,1H),5.02–5.58 (m,5H), 5.85–5.98 (m,2H),6.65–6.92 (m,3H),7.20–7.42 (m,5H)

Preparation 120

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.4 g) was used instead of HCl.H-MeLeu-D-Lac-OBz. Except above matter. Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.05 (m,24H),1.15–1.90 (m,2.7H),2.62–3.15 (m,16H), 4.60–5.60 (m,10H),5.85–5.96 (m,4H),6.60–6.80 (m,6H),7.26–7.40 (m,5H)

Preparation 121

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.59 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.59 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.75–1.00 (m,24H),1.15–1.82 (m,2.7H),2.62–3.20 (m,16H), 4.56–5.63 (m,8H),5.92 (s,4H),6.60–6.80 (m,6H)

Preparation 122

To a solution of 3-nitro-L-tyrosine (4.52 g) in dioxane (40 ml) was added 1N sodium hydroxide solution (40 ml), and further di-t-butyldicarbonate (4.8 g) was added and stirred for 1 hour at room temperature. To the reaction was added water (200 ml) and extracted with ethyl acetate (100 ml×3).

After the ethyl acetate layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give N-(t-butoxycarbonyl)-3-nitro-L-tyrosine (6.50 g).

NMR ($CDCl_3$,δ):1.42 (s,9H),2.9–3.3 (m,3H),4.6–4.65 (m) and 5.05 –5.15 (m) (1H),7.09 (d,1H),7.44 (dd,1H),7.93 (d,1H),10.4–10.6 (m,1H)

IR (KBr): 1713,1683 cm^{-1}

Preparation 123

To a solution of N-(t-butoxycarbonyl)-3-nitro-L-tyrosine (6.49 g) in dimethylformamide (50 ml) was added potassium carbonate (11.05 g). Further methyl iodide (3.7 ml) was added and stirred for 15 hours at room temperature. To the reaction solution was added water (500 ml) and extracted with ethyl acetate (100 ml×3). After ethyl acetate layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give methyl N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.76 g).

NMR ($CDCl_3$,δ): 1.42 (s,9H),3.00 (dd,1H)),3.17 (dd,1H), 3.75 (s,3H),3.95 (s,3H),4.5–4.65 (m) and 5.0–5.1 (m) (1H), 7.02 (d,1H),7.33 (dd,1H),7.62 (d,1H)

IR (KBr): 1742,1710,1695 cm^{-1}

Preparation 124

To a ethanol solution of methyl N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.74 g) was added 1N sodium hydroxide solution (25 ml) and was stirred for 2 hours at room temperature. The solvent was evaporated and water (70 ml) and 1N hydrochloric acid solution (27.5 ml) was added, extracted with ethyl acetate (50 ml×3). After ethyl acetate layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give N-(t-butoxycarbonyl) -O-methyl-3-nitro-L-tyrosine (6.61 g).

NMR ($CDCl_3$,δ): 1.42 (s,9H),2.9–3.3 (m,2H),3.95 (s,3H), 4.5–4.65 (m) and 5.0–5.1 (m) (1H),7.27 (d,1H),7.39 (dd, 1H)),7.69(bs,1H)

IR (KBr): 1727,1652 cm^{-1}

Preparation 125

To N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.60 g) was added 4N hydrogen chloride in ethyl acetate solution and was stirred for 1 hour at room temperature. The solvent was evaporated and further it was azeotroped by toluene to give O-methyl-3-nitro-L-tyrosine hydrochloride (4.95 g).

NMR (DMSO-d_6,δ): 3.1–3.2 (m,2H),3.92 (s,3H),4.21 (t,1H),7.35 (d,1H), 7.59 (dd,1H),7.83 (d,1H)

IR (KBr): 1729 cm^{-1}

Preparation 126

To suspension solution of O-methyl-3-nitro-L-tyrosine-.hydrochloride (4.93 g) in 6N aqueous hydrochloric acid was added under ice-cooling, sodium nitrite (1.97 g) and was stirred at the same temperature for 1 and ½ hour and further at room temperature for 3 hours. The resultant suspension solution was extracted with ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to give (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionic acid (4.46 g).

NMR ($CDCl_3$,δ): 3.21 (dd,1H),3.39 (dd,1H),3.96 (s,3H), 4.49 (dd,1H) 7.06 (d,1H),7.45 (dd,1H),7.77 (d,1H)

IR (neat): 1726 cm^{-1}

Preparation 127

To a ethanol solution of (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionic acid (4.46 g) was added p toluenesulfonic acid (0.38 g) and heated under reflux for 5 hours. After cooled it down, the solvent was evaporated in vacuo. The resultant suspension solution was extracted by ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane or ethyl acetate (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionate (4.51 g)

NMR ($CDCl_3$,δ): 1.26 (t,3H),3.17 (dd,1H),3.36 (dd,1H)), 3.96 (s,3H),4.15 (q,2H),4.41 (dd,1H) 7.03 (d,1H),7.43 (dd, 1H),7.74 (d,1H)

IR (neat): 1735 cm^{-1}

Preparation 128

To a ethanol solution (50 ml) which contain acetic acid (2.3 ml) was added cesium carbonate (6.5 g) and stirred for a half an hour at room temperature, and the solvent was evaporated to give cesium acetate. Cesium acetate was added to dimethylformamide solution of ethyl (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionate (4.51 g) and stirred for 4 hours. To the mixture, water (200 ml) was added and extracted with ether (100 ml×1, 50 ml×2). After ether layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate and evaporated in vacuo. The resultant crude product was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-2-acetoxy-3-(4-methoxy-3-nitrophenyl)propionate (1.58 g).

NMR ($CDCl_3$,δ): 1.26 (t,3H),2.11 (s,3H),3.05–3.25 (m,2H),3.95 (s,3H), 4.20 (q,2H),5.19 (dd,1H) 7.03 (d,1H), 7.42 (dd,1H),7.74 (d,1H)

IR (neat): 1742 cm^{-1}

Preparation 129

To a ethanol solution (50 ml) which contain 37% aqueous formalin solution (4.0 ml) of ethyl (R)-2-acetoxy-3-(4-methoxy-3-nitrophenyl)propionate (1.56 g) was added 10% palladium on carbon (0.5 g) and under atmospheric pressure hydrogenated at room temperature for 4 hours. The catalyst was filtered off and the solvent was evaporated in vacuo. The resultant crude product was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-2-acetoxy-3-(4-methoxy-3-dimethylaminophenyl-)propionate (1.58 g).

NMR ($CDCl_3$,δ): 1.23 (t,3H),2.09 (s,3H),2.77 (s,6H), 2.95–3.15 (m,2H), 3.87 (s,3H),4.18 (q,2H),5.15 (dd,1H) 6.75–6.9 (m,3H)

IR (neat): 1742 cm^{-1}

Preparation 130

To a solution of ethyl (R)-2-acetoxy-3-(4-methoxy-3-dimethylaminophenyl)propionate (1.56 g) in benzyl alcohol (3.7 ml) and benzene (7.4 ml) was added p-toluenesulfonic acid (0.82 g) and heated under reflux for 6 hours. After cooling, the solvent was evaporated in vacuo, and the gained crude product was purified by silica gel column chromatography. The residue was eluted with mixed solvent of hexane, ethyl acetate, and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-methoxy-3-dimethylaminophenyl)propionate (0.93 g).

NMR ($CDCl_3$,δ): 2.68 (d,1H),2.74 (s,6H),2.92 (dd,1H), 5.19 (s,2H) 6.7–6.8 (m,3H),7.3–7.4 (m,5H)

IR (KBr): 1738 cm^{-1}

Preparation 131

H-D-3MA-4MOPhLac-OBzl (0.90 g) was used instead of H-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.40 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.41 (s) and 1.47 (s) (9H), 1.4–1.6 (m,3H), 2.65 (s) and 2.68 (s) (3H),2.75 (s,6H), 3.1–3.2 (m,2H),3.85 (s,3H),4.6–4.75 (m) and 4.95–5.3 (m) (4H),6.7–6.8 (m,3H),7.2–7.4 (m,5H)

IR (KBr): 1741,1695 cm^{-1}

Preparation 132

Boc-MeLeu-D-3MA-4MOPhLac-OBzl (1.38 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-OH (1.16 g) was obtained according to a similar manner to that of Preparation 25.,

IR (KBr): 1740,1694 cm^{-1}

Preparation 133

Boc-MeLeu-D-3MA-4MOPhLac-OH (1.16 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.80 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.1 (m,12H),1.35–1.7 (m,18H), 2.65–3.1 (m,12H), 3.0–3.1 (m,2H),3.85 (s,3H),4.60–3.8 (m) and 4.9–5.5 (m) (6H), 6.7–6.85 (m,3H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1664 cm^{-1}

Preparation 134

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.90 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (0.85 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1696,1662 cm^{-1}

Preparation 135

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.90 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.97 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1648 cm^{-1}

Preparation 136

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (0.84 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and 2HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.96 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.15 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.05 (m,24H),1.3–1.8 (m,2.7H), 2.6–3.2 (m,16H), 2.77 (s,12H),3.85 (s,6H),4.65–4.75 (m) and 4.9–5.5 (m) (10H),6.7–6.9 (m,6H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1663 cm^{-1}

FAB-MS: 1303 $[M+H]^+$

Preparation 137

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.14 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.09 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1694,1663 cm^{-1}

Preparation 138

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.08 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.19 g) was obtained according to a similar manner to that of

Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

Preparation 139

To a dichloromethane solution of ethyl D-2-hydroxy-3-(4-aminophenyl)propionate (4.2 g) were added under ice-cooling, triethylamine (7.36 ml), acetyl chloride (2.5 g) at room temperature for 2 and ½ hours. The reaction solution was poured into aqueous saturated sodium bicarbonate solution, and extracted with dichloromethane. After drying by magnesium sulfate, the solvent was evaporated in vacuo and then purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-3-(4-acetamidephenyl)-2-acetoxypropionate (3.42 g).

NMR ($CDCl_3$,δ): 1.24 (t,3H),2.08 (s,3H),2.16 (s,3H), 3.06–3.20 (m,2H), 4.17 (q,2H),5.12–5.20 (m,1H),7.17 (d,2H),7.43 (d,2H)

Preparation 140

To an anhydrous acetic acid solution of ethyl (R)-3-(4-acetamidephenyl)-2-acetoxypropionate (3.12 g) was added dropwise under ice-cooling, fuming nitric acid (3 ml)—acetic anhydride (7.5 ml), and stirred for a half an hour successively. The reaction solution was poured into aqueous saturated sodium bicarbonate solution, after the neutralization, extracted with ethyl acetate, and washed with saturated brine. After drying by magnesium sulfate, the solvent was evaporated in vacuo to give ethyl (R)-3-(4-acetamide-3-nitrophenyl)-2-acetoxypropionate (3.98 g)

NMR ($CDCl_3$,δ): 1.25 (t,3H),2.11 (s,3H),2.29 (s,3H), 3.10–3.25 (m,2H), 4.50 (q,2H),5.17–5.24 (m,1H),7.52 (dd, 1H),8.10 (d,1H),8.72 (d,1H)

Preparation 141

To a solution of ethyl (R)-3-(4-acetamide-3-nitrophenyl)-2-acetoxypropionate (3.9 g) in ethanol (120 ml) was added concentrated hydrochloric acid and heated under reflux for 75 minutes. After ethanol was evaporated in vacuo, aqueous saturated sodium bicarbonate solution was added, extracted with ethyl acetate, and washed with saturated sodium chloride. After drying by magnesium sulfate, the solvent was evaporated in vacuo to give ethyl (R)-3-(4-amino-3-nitrophenyl)-2-hydroxypropionate (2.59 g).

NMR ($CDCl_3$,δ): 1.32 (t,3H),2.89 (dd,1H),3.05 (dd,1H), 4.23 (q,2H),4.35–4.50 (m,1H),6.74 (d,1H),7.30 (dd,1H)), 7.30 (d,1H)

Preparation 142

To a solution of ethyl (R)-3-(4-amino-3-nitrophenyl)-2-hydroxypropionate (0.8 g) in methanol (8 ml) and water (5 ml) were added iron powder (1 g), acetic acid (0.8 ml) and heated under reflux for a half an hour. After the reaction solution was filtered through celite, methanol was evaporated in vacuo. After the residue was neutralized with aqueous sodium bicarbonate solution, the residue was extracted with ethyl acetate. After drying by magnesium sulfate, the solvent was evaporated in vacuo, and dissolved in acetic acid. To the mixture paraformaldehyde (0.56 g), and sodium cyanoborohydride (0.59 g) were added and stirred for 19 hours at room temperature. The reaction

solution was added to aqueous solution saturated with sodium bicarbonate, and after the residue was neutralized with aqueous sodium bicarbonate solution, extracted with ethyl acetate, and dried over sodium sulfate. The solvent was evaporated in vacuo and then purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (3:2, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-3-[3,4-bis (dimethylamino)phenyl]-2-hydroxypropionate (0.3 g).

NMR ($CDCl_3$,δ): 1.29 (t,3H),2.65 (s,6H),2.77 (s,6H), 2.75–3.16 (m,2H), 4.23 (q,2H),4.35–4.50 (m,1H),6.70–6.83 (m,2H),7.21–7.26 (m,1H)

El-MS: 281 $[M]^+$

Preparation 143

To a solution of ethyl (R)-3-[3,4-bis(dimethylamino)phenyl]-2-hydroxypropionate (0.54 g) in benzene were added benzyl alcohol (2 ml) and 13-toluenesulfonic acid (0.8 g) and heated under reflux for 5 hours. The reaction solution was added to aqueous dilute hydrochloric acid, after washing with ethyl acetate, the water layer was neutralized with aqueous saturated sodium bicarbonate, and extracted with ethyl acetate. After washing with saturated sodium chloride, dried over sodium sulfate. After the solvent was evaporated in vacuo, purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (3:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (12)-3-[3,4-bis(dimethylamino)phenyl]-2-hydroxypropionate (0.3 g).

NMR ($CDCl_3$,δ): 2.74 (s,6H),2.75 (s,6H),2.91 (dd,1H), 3.05 (dd,1H),4.40–4.55 (m,1H),5.15 (d,1H),5.22 (d,1H), 6.60–6.80 (m,3H),7.25–7.40 (m,5H)

IR (KBr): 1734 cm^{-1}

Preparation 144

H-D-3,4-DMAPhLac-OBzl (0.32 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.32–1.60 (m,12H), 2.60–2.70 (m,3H),2.75 (s,12H),3.00–3.20 (m,2H),4.62–5.30 (m,4H),6.65–6.78 (m,3H),7.20–7.40 (m,5H)

Preparation 145

Boc-MeLeu-D-3,4-DMAPhLac-OBzl (0.59 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-OH (0.47 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.20–1.80 (m,12H), 2.60–2.85 (m,15H), 3.00–3.28 (m,2H),4.30–4.80 (m) and 5.18–5.37 (m) (2H),6.78–6.90 (m,3H)

Preparation 146

Boc-MeLeu-D-3,4-DMAPhLac-OH (0.47 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.67 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.00 (m,12H),1.38–1.70 (m,18H), 2.71–3.18 (m,20H), 4.60–5.57 (m,6H),6.66–6.80 (m,3H), 7.22–7.38 (m,5H)

Preparation 147

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.30 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.08 (m,12H),1.20–1.75 (m,18H), 2.62–3.23 (m,20H), 4.60–5.82 (m,4H),6.72–6.84 (m,3H)

Preparation 148

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.33 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.30 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.76–1.12 (m,12H),1.25–2.20 (m,9H), 2.60–4.20 (m,21H), 5.05–5.60 (m,5H),7.20–7.62 (m,7H), 8.30–8.50 (m,1H),9.42–9.70 (m,1H),10.92–11.20 (m,1H)

Preparation 149

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.30 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 3HCl.H-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.30 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.35 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.78–1.00 (m,24H),1.20–1.80 (m,2.7H),2.63–3.18 (m,40H), 4.90–5.60 (m,10H),6.65–6.80 (m,6H),7.22–7.38 (m,5H)

FAB-MS: 1330 $[M+H]^+$

Preparation 150

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMAPhLac-MeLeu-D-m-Lac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.35 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.07 (m,24H),1.10–1.80 (m,27H), 2.30–3.20 (m, 40H),4.60–5.74 (m,8H),6.70–6.82 (m,6H)

Preparation 151

(S)-2-fluorophenyl alanine (3.00 g) was dissolved in 6N -aqueous hydrochloric acid (80 ml) and at 0° C. sodium nitrite (3.01 g) was added gradually. After the mixture was stirred for 4 hours successively, the temperature was increased back to room temperature. To the mixture was added sodium nitrite (1.13 g), stirred further for 2 hours, added water (200 ml), and extracted with ether (150 ml×1, 100 ml×2). The ether layer was washed with a solution (saturated brine: water=1:1, v/v) (100 ml×2), dried over calcium chloride, and the solvent was evaporated in vacuo. To the residue, benzene (20 ml), benzylalcohol (1.32 ml) and p-toluenesulfonic acid mono hydrate (0.33 g) were added and heated under reflux for an hour using Dean-stark apparatus. After cooling down to room temperature, the crude product, which was gained by evaporating the solvent, was purified by silica gel chromatography, eluting with a mixed solvent of ethyl acetate and hexane (1:19 V/V). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (S)-2-chloro-3-(2-fluorophenyl)propionate (2.24 g).

NMR ($CDCl_3$,δ): 3.25 (dd,1H),3.40 (dd,1H),4.57 (t,1H), 5.16 (s,2H),6.98– 7.40 (m,9H)

EI-MS: 292 $[M]^+$

Preparation 152

Benzyl (S)-2-chloro-3-(2-fluorophenyl)propionate (0.90 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-o-FPhLac-OBzl (1.30 g) was obtained according to a similar matter to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.38–1.63 (m,12H), 2.58–2.70 (m,3H),3.10– 3.38 (m,2H),4.6–4.78 (m) and 5.1–5.38 (m) (4H),6.97–7.42 (m,9H)

FAB-MS: 402 [M-Boc+H]$^+$

Preparation 153

Boc-MeLeu-D-o-FPhLac-OBzl (1.26 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-OH (1.07 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.02 (m,6H),1.19–1.82 (m,12H), 2.63–2.88 (m,3H), 3.08–3.9 (m,2H),4.26–4.42 (m) and 4.6–4.8 (m) and 5.23–5.44 (m) (2H),6.99–7.4 (m,4H)

Preparation 154

Boc-MeLeu-D-o-FPhLac-OH (1.03 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (1.45 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.05 (m,12H),1.18–1.83 (m,18H), 2.7–3.2 (m,8H), 4.6–4.8 (m) and 4.88–5.6 (m) (6H), 6.99–7.43 (m,9H)

FAB-MS: 601 [M-Boc+H]$^+$

Preparation 155

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.70 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.57 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.03 (m,12H),1.08–1.85 (m,18H), 2.59–3.38 (m,8H), 4.6–4.98 (m) and 5.05–5.6 (m) and 5.83–6.0 (m) (4H),6.99–7.38 (m,4H)

Preparation 156

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.61 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.53 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.62–1.03 (m,12H),1.2–2.05 (m,9H), 2.58–2.75 (m, 3H),2.98–3.36 (m,5H),3.62–3.82 (m,1H), 5.02–5.38 (m) and 5.46–5.63 (m) (5H),6.99–7.43 (m,9H)

Preparation 157

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.55 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.51 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.97 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$, δ): 0.78–1.04 (m,24H),1.10–1.82 (m,27H),2.7–3.23 (m,16H), 4.6–4.8 (m) and 5.02–5.61 (m) (10H),6.98–7.42 (m,13H)

FAB-MS: 1093 [M-Boc+H]$^+$

Preparation 158

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.89 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.84 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.05 (m,24H),1.12–1.82 (m,27H), 2.62–3.29 (m,16H), 4.5–5.87 (m,8H),6.98–7.38 (m,8H)

Preparation 159

(S)-3-fluorophenylaniline (5.20 g) was used instead of (S)-2-fluorophenylaniline. Except above matter, benzyl (S)-2-chloro-3-(3-fluorophenyl) propionate (7.04 g) was obtained according to a similar manner to that of Preparation 151.

NMR ($CDCl_3$,δ): 3.17 (dd,1H),3.36 (dd,1H)),4.47 (t,1H), 5.17 (s,2H),6.82–7.04 (m,3H),7.18–7.5 (m,6H)

EI-MS: 292 [M]$^+$

Preparation 160

Benzyl (S)-2-chloro-3-(3-fluorophenyl)propionate (1.76 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-m-FPhLac-OBzl (1.13 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.9 (d,6H),1.39–1.78 (m,12H),2.6–2.77 (m,3H),3.03–3.22 (m,2H),4.63–4.79 (m) and 4.92–5.36 (m) (4H),6.8–7.0 (m,3H), 7.18–7.42 (m,6H)

FAB-MS: 402 [M-Boc+H]$^+$

Preparation 161

Boc-MeLeu-D-m-FPhLac-OBzl (1.11 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-OH (1.00 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.00 (m,6H),1.2–1.8 (m,12H), 2.76–2.85 (m,3H), 3.02–3.25 (m,2H),4.38–4.5 (m) and 4.62–4.79 (m) and 5.19–5.41 (m) (2H),6.86–7.04 (m,3H), 7.19–7.38 (m,1H)

Preparation 162

Boc-MeLeu-D-m-FPhLac-OH (0.99 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.01 (m,12H),1.39–1.79 (m,18H), 2.73–3.18 (m,8H), 5.03–5.57 (m,6H),6.88–7.07 (m,3H), 7.21–7.42 (m,6H)

FAB-MS: 601 [M-Boc+H]$^+$

Preparation 163

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.69 g) was obtained according to a similar manner to that of

Preparation 25.

NMR CCDCl_3,δ): 0.8–1.02 (m,12H),1.1–1.8 (m,18H), 2.63–3.3 (m,8H), 4.62–5.59 (m) and 5.73–5.85 (m) (4H), 6.83–7.1 (m,3H),7.19–7.38 (m,1H)

Preparation 164

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.69–1.03 (m,12H),1.18–2.03 (m,9H), 2.58–2.7 (m,3H), 2.82–3.0 (m,3H),3.03–3.21 (m,2H), 3.62–3.82 (m,1H),5.01–5.38 (m) and 5.41–5.58 (m) (5H), 6.94–7.07 (m,3H),7.17–7.43 (m,6H)

Preparation 165

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.69 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, HCl.H-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.59 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.04 (m,24H),1.04–1.95 (m,27H), 2.6–3.3 (m,16H), 4.62–4.79 (m) and 4.88–5.58 (m) (10H), 6.82–7.14 (m,6H),7.19–7.42 (m,7H)

FAB-MS: 1094 [M-Boc+H]$^+$

Preparation 166

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-Do-m-FPhLac-MeLeu-D-Lac-OBzl (0.97 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter,

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.77–1.05 (m,24H),1.05–1.83 (m,27H), 2.58–3.22 (m,16H), 4.6–4.79 (m) and 4.88–5.78 (m) (8H), 6.85–7.08 (m,6H),7.18–7.39 (m,2H)

Preparation 167

(S)-4-fluorophenylaniline (5.00 g) was used instead of (S)-2-fluorophenylaniline. Except above matter, benzyl (S)-2-chloro-3-4-fluorophenyl) propionate (1.8 g) was obtained according to similar manner to that of Preparation 151.

NMR ($CDCl_3$,δ): 3.16 (dd,1H),3.33 (dd,1H),4.44 (t,1H), 5.15 (s,2H),6.88–7.42 (m,9H)

El-MS: 292 $[M]^+$

Preparation 168

Benzyl (S)-2-chloro-3-(4-fluorophenyl)propionate (2.21 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-p-FPhLac-OBzl (1.55 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.9 (d,6H),1.3–1.62 (m,12H),2.58–2.67 (m,3H),3.0–3.12 (m,2H),4.6–4.79 (m) and 4.9–5.27 (m) (4H),6.9–7.42 (m,9H)

FAB-MS: 402 $[M\text{-}Boc+H]^+$

Preparation 169

Boc-MeLeu-D-p-FPhLac-OBzl (1.45 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-OH (1.25 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.83–1.00 (m,6H),1.41–1.78 (m,12H), 2.7–2.84 (m,3H), 3.02–3.23 (m,2H),4.41–5.39 (m,3H), 6.9–7.06 (m,2H),7.1–7.26 (m,2H)

Preparation 170

Boc-MeLeu-D-p-FPhLac-OH (1.23 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (2.06 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.7–1.04 (m,12H),1.1–1.97 (m,18H), 2.63–2.96 (m,6H), 3.0–3.18 (m,2H),4.6–5.5 (m,6H), 6.88–7.1 (m,2H),7.15–7.5 (m,7H)

FAB-MS: 601 $[M\text{-}Boc+H]^+$

Preparation 171

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.9 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.78 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.8–1.02 (m,12H),1.05–1.8 (m,18H), 2.62—3.3 (m,8H), 4.6–5.85 (m,4H),6.88–7.05 (m,2H), 7.12–7.28 (m,2H)

Preparation 172

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.89 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.85 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.68–1.05 (m,12H),1.18–2.05 (m,9H), 2.53–2.68 (m,3H), 2.82–3.0 (m,3H),3.0–3.18 (m,2H), 3.63–3.81 (m,1H),5.02–5.38 (m,4H), 5.4–5.59 (m,1H), 6.96–7.07 (m,2H),7.15–7.42 (m,7H)

Preparation 173

Boc-MeLeu-D -p-FPhLac-MeLeu-D-Lac-OH (0.77 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.84 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.78–1.07 (m,24H),1.13–1.9 (m,27H), 2.62–3.28 (m,16H), 4.6–4.8 (m) and 4.9–5.57 (m) (10H), 6.86–7.07 (m,4H),7.07–7.42 (m,9H)

FAB-MS: 1094 $[M\text{-}Boc+H]^+$

Preparation 174

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (1.31 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.99 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.05 (m,24H),1.18–1.93 (m,27H), 2.62–3.24 (m,16H), 4.58–5.8 (m,8H),6.88–7.04 (m,4H), 7.1–7.38 (m,4H)

Preparation 175

Boc-MeLeu-D)-p-MeOPhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.42 g) was used instead of, HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.28 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.02 (m,24H),1.02–1.96 (m,27H), 2.6–3.25 (m,16H), 3.78 (s,3H),4.6–4.8 (m) and 4.95–5.57 (m) (10H),6.78–6.90 (m,2H), 7.04–7.4 (m,12H)

FAB-MS: 1087 $[M\text{-}Boc+H]^+$

Preparation 176

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.13 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OH (0.98 g)was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.72–1.04 (m,24H),1.04–1.9 (m,27H), 2.6–3.25 (m,16H), 3.78 (s,3H),4.58—4.8 (m) and 4.82–5.56 (m) and 5.65–5.82 (m) (8H),6.78–6.9 (m,2H),7.03–7.38 (m,7H)

Preparation 177

Benzyl chloroacetate (1.85 g) was used instead of benzyl (S)- 2-chloro-3-(4-methoxyphenyl)propionate. Except above matter, Boc-MeLeu-Glycol-OBzl (4.0 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.93 (d,6H),1.45 (s,9H),1.4–1.8 (m,3H),2.78 (s) and 2.80 (s) (3H),4.6–5.0 (m,3H),5.29 (s,2H),7.35 (s,5H)

IR (KBr): 1740,1695 cm^{-1}

Preparation 178

Boc-MeLeu-Glycol-OBzl (1.50 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-Glycol-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1753 cm^{-1}

Preparation 179

Boc-MeLeu-D-p-MeOPhLac-OH (0.69 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-Glycol-OBzl (0.59 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.79 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.0 (m,12H),1.2–1.8 (m,6H),1.42 (s) and 1.47 (s) (9H),2.7–3.0 (m,6H),3.03 (d,2H),3.78

(s,3H),4.66 (s,2H),4.6–5.5 (m, 3H),5.28 (s,2H),6.82 (d,2H), 7.14 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1664 cm^{-1}

APCI-MS: 599 $[M+H]^+$

Preparation 180

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.32 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1744,1691,1663 cm^{-1}

Preparation 181

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.38 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1745,1653 cm^{-1}

Preparation 182

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.32 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.37 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.603 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.05 (m,24H),1.41 (s) and 1.47 (s) (9H),1.21–1.9 (m,12H),2.65–3.1 (m,16H),3.78 (s,6H), 4.60–4.85 (m) and 5.15– 5.5 (m) (10H),5.16 (s,2H), 6.75–6.90 (m,2H),7.05–7.2 (m,2H),7.3–7.4 (m,5H)

IR (KBr): 1744,1689,1667 cm^{-1}

FAB-MS: 1189M+H]$^+$

Preparation 183

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.58 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.55 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): **1742, 1664**cm^{-1}

Preparation 184

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.55 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.53 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

EXAMPLE 1

To a solution of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OC $_6F_5$ (0.4 g) in methylene chloride (4 ml) was added under ice-cooling, trifluoroacetic acid (2 ml) and stirred for 2 hours successively. The solvent was evaporated in vacuo, and the residue was dissolved in dioxane (30 ml). After adding the mixture dropwise for 5 hours into pyridine (629 ml) which was heated at 90° C., it was stirred for 2 and ½ hours successively. The solvent was evaporated in vacuo, azeotroped by toluene (30 ml). To the residue was added ethyl acetate (200 ml), washed with 10% aqueous citric acid solution, water, aqueous saturated sodium bicarbonate solution, water in order, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1.5:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MeOPhLac-MeLeu—D-Lac-MeLeu—D-p-MeOPhLac-MeLeu—D-Lac

(0.16 g).

NMR ($CDCl_3$,δ): 0.79–1.00 (m,24H), 1.10–1.80 (m,18H), 2.73–3.09 (m,16H), 3.78 (s,6H), 4.40–4.54 (m), and 5.00–5.67 (m) (8H), 6.82 (d, 4H), 7.15 (d,4H).

IR (KBr): 1741,1662 cm^{-1}

FAB-MS: 1009 $(M+H)^+$

EXAMPLE 2

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OC $_6F_5$ was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OC$_6$F $_5$. Except above matter,

MeLeu—D-Man-MeLeu—D-Lac-MeLeu—D-Man-MeLeu—D-Lac

(0.11 g) was obtained according to a similar manner to that of Example 1.

NMR ($CDCl_3$,δ): 0.70–1.00 (m,24H), 1.10–1.98 (m,18H), 2.75–3.10 (m,12H),4.60–5.70 (m,6H), 6.44 (s,2H),7.30–7.60 (m,10H).

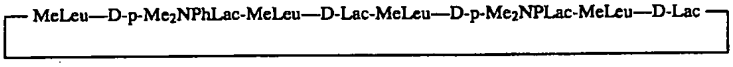
IR (KBr): 1750,1677 cm^{-1},

FAB-MS: 921 $(M+H)^+$

EXAMPLE 3

To a solution of 3HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.825 g) in dichloromethane was (700 ml) was added under ice-cooling, triethylamine (0.45 ml) and bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.27 g), and stirred for 14 hours successively, and further stirred for 4 hours at room temperature. The solvent was evaporated in vacuo, was added water (50 ml), and extracted with ethyl acetate (40 ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate and ethanol (60:35:5, v/v). The

fractions containing the desired product were combined and evaporated in vacuo to obtain



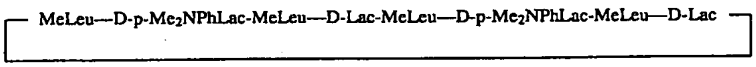
(0.40 g).

NMR ($CDCl_3$,δ) 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m,28H), 4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

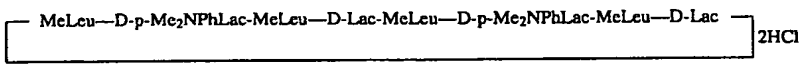
FAB-MS: 1035 $[M+H]^+$

EXAMPLE 4



(0.145 g)
was dissolved in 4N-hydrogen chloride in ethyl acetate (2 ml).

The solvent was evaporated in vacuo, the residue was dissolved in 4N-hydrogen chloride in ethyl acetate (2 ml) again. After the solvent was evaporated in vacuo, azeotroped by toluene (10 ml) twice to give



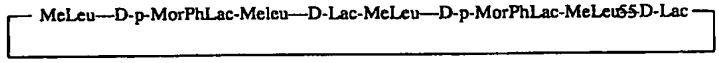
(0.157 g).

NMR ($CDCl_3$,δ) 0.7–1.1 (m,24H),1.25–1.85 (m,18H), 2.8–3.4 (m,16H), 3.15 (bs,12H),4.6–5.75 (m,8H),7.35–7.5 (m,4H),7.6–7.75 (m,4H)

IR (KBr): 1742,1649 cm^{-1}

EXAMPLE 5

To a solution of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.404 g) in dichloromethane (162 ml) were added sodium bicarbonate (0.27 g) and bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.13 g), and stirred for 71 hours successively. The solvent was evaporated in vacuo, added water (50 ml), and extracted with ethyl acetate (50ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate, and ethanol (50:45:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain



(0.238 g).

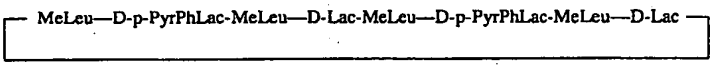
NMR ($CDCl_3$,δ) 0.8–1.1 (m,24H),1.3–1.8 (m,18H), 2.7–3.2 (m,24H), 3.8–3.9 (m,8H),44–4.55 (m) and 5.0–5.7 (m) (8H),6.82 (d,4H),7.13 (d, 4H)

IR (KBr): 1740, 1662 cm^{-1}

FAB-MS : 1119 $[M+H^+$

EXAMPLE 6

3HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.80 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,



(0.238 g) was obtained according to a similar manner to that of

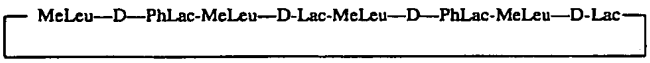
EXAMPLE 5.

NMR ($CDCl_3$,δ) 0.75–1.1 (m,24H),1.2–1.8 (m,18H), 1.9–2.05 (m,8H), 2.7–3.1 (m,16H),3.15–3.3 (m,8H), 4.4–4.55 (m) and 5.0–5.7 (m) (8H), 6.46 (d,4H),7.06 (d,4H)

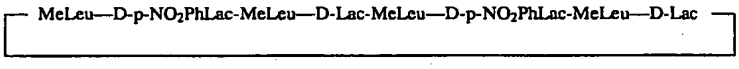
IR (KBr): 1740,1664 cm^{-1}

FAB-MS: 1087 $[M+H]^+$

EXAMPLE 7



(0.382 g) was cooled down to −10° C. After fuming nitric acid (3.5 ml) was added dropwise in 15 minutes, the mixture was stirred for one hour at room temperature. The reaction solution was added gradually into saturated sodium bicarbonate (25 ml), and extracted with ethyl acetate (25 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo to give crude product of



(0.465 g).

NMR ($CDCl_3$; δ) 0.65–1.1 (m,24H),1.2–1.8 (m,18H), 2.7–3.3 (m,16H), 44–4.55 (m) and 5.0–5.7 (m) (8H), 7.35–7.55 (m,4H),8.05–8.15 (m, 4H)

IR (KBr): 1742,1662,1519,1343 cm^{-1}

FAB-MS: 1039 $[M+H]^+$

EXAMPLE 8

To a ethanol (5 ml) solution of crude product (72 mg) of

MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac

were added 37% aqueous formaldehyde (0.4 ml) and 10% palladium on carbon (0.1 g), and hydrogenated for 2 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate and ethanol (75:20:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-Me_2NPhLac-MeLeu—D-Lac-MeLeu—D-p-Me_2NPhLac-MeLeu—D-Lac

(42 mg).

NMR ($CDCl_3$; δ) 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m,28H), 4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

EXAMPLE 9

To a methanol (10 ml) solution of crude product (312 mg) of

MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac

was added 10% palladium on carbon (0.1 g), and hydrogenated for 2 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate and ethanol (40:55:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(144 mg).

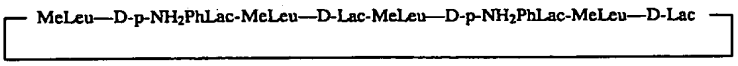
NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m, 16H),4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

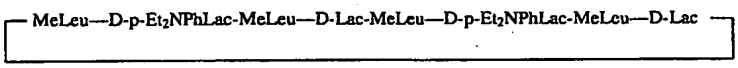
FAB-MS: 979 $[M+H]^+$

EXAMPLE 10

To a methanol (10 ml) solution of



(250 mg) were added acetaldehyde (0.56 g) and 10% palladium on carbon (0.15 g), and hydrogenated for 4 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (25:20:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain



(147 mg).

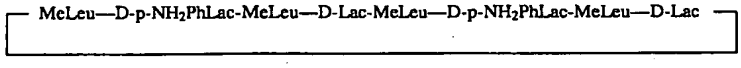
NMR ($CDCl_3$,δ): 0.7–1.9 (m,54H),2.65–3.1 (m,12H), 3.2–3.4 (m,8H), 4.4–4.5 (m) and 5.0–5.8 (m) (8H),6.45–6.6 (m,4H),7.0–7.1 (m,4H)

IR (KBr):1741,1662 cm^{-1}

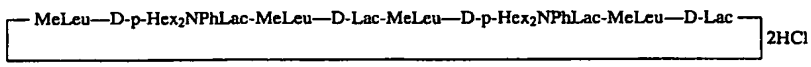
FAB-MS: 1091 $[M+H]^+$

EXAMPLE 11

To a methanol (10 ml) solution of



(250 mg) were added n-hexanal (0.62 g) and 10% palladium on carbon (0.15 g), and hydrogenated for 11 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (25:70:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo. To the resultant residue was added 4N-hydrogen chloride in ethyl acetate (5 ml), and the solvent was evaporated, repeated the same procedure again to give



(147 mg).

NMR ($CDCl_3$,δ): 0.7–2.1 (m,86H),2.7–3.6 (m,24H), 4.4–4.6 (m) and 5.0–5.7 (m) (8H),7.3–7.45 (m,4H),7.6–7.75 (m,4H)

IR (KBr): 1743,1656 cm^{-1}

FAB-MS: 1315 $[M+H]^+$

EXAMPLE 12

3HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.24 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-PipPhLac-MeLeu—D-Lac-MeLeu—D-p-PipPhLac-MeLeu—D-Lac

(0.82 g) was obtained according to a similar manner to that of Example 5.

NMR ($CDCl_3$,δ): 0.7–1.1 (m,24H),1.2–1.9 (m,30H), 2.65–3.2 (m,24H), 4.4–4.55 (m) and 5.0–5.7 (m) (8H),6.84 (d,4H),7.09 (d,4H)

IR (KBr): 1740,1663 cm^{-1}

FAB-MS: 1115 $[M+H]^+$

EXAMPLE 13

A suspension of

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(0.228 g),2,5-dimethoxytetrahydrofuran (0.045 ml) and acetic acid (1 ml) were stirred for 3 hours at room temperature, and further stirred for 3 hours at 50° C. Further more, to the mixture was added 2,5-dimethoxytetrahydrofuran (0.045 ml) and stirred for 3 hours successively. The reaction solution was poured into ice-aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate (20 ml×2). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (50:45:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-PylPhLac-MeLeu—D-Lac-MeLeu—D-p-PylPhLac-MeLeu—D-Lac

(56.6 mg).

NMR ($CDCl_3$,δ): 0.77–1.1 (m,24H),1.2–1.82 (m,18H), 2.7–3.23 (m, 16H),52–5.73 (m,8H),6.28–6.39 (m,4H), 6.56–6.7 (m,4H),6.96–7.38 (m, 8H)

IR (KBr): 1742,1663 cm^{-1}

FAB-MS: 1079 $[M+H]^+$

EXAMPLE 14

To a trifluoroacetic acid (0.5 ml) solution of

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(48 mg) was added at room temperature, sodium nitrite (8 mg), after the reaction solution was stirred for 1 hour at 60° C., the solvent was evaporated in vacuo and the residue was azeotroped by toluene. To the residue were added sodium bicarbonate (84 mg), water (0.5 ml), dioxane (2.5 ml) and after the mixture was stirred for 15 hours at room temperature, water (50 ml) was added and extracted with ethyl acetate (25 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (65:30:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(40.4 mg).

NMR ($CDCl_3$,δ): 0.70–1.8 (m,42H),2.7–3.15 (m,16H), 4.38–4.55 (m) and 4.97–5.68 (m) (8H),6.65–6.83 (m,4H), 6.94–7.17 (m,4H)

IR (KBr): 1741,1648 cm^{-1}

FAB-MS: 981 $[M+H]^+$

EXAMPLE 15

A suspension of

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(0.3 g), dimethylformamide (2 ml), potassium carbonate (128.5 mg) and ethyl iodide (0.08 ml) were stirred for 18 hours at room temperature, and then water (30 ml) was added and extracted with ethyl acetate (20 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-EtOPhLac-MeLeu—D-Lac-MeLeu—D-p-EtOPhLac-MeLeu—D-Lac

(0.188 g).

NMR ($CDCl_3$,δ): 0.76–1.09 (m,24H),1.3–1.82 (m,16H), 2.7–3.15 (m, 16H),3.99 (q,4H),4.4–4.58 (m) and 4.9–5.8 (m) (8H),6.76–6.88 (m,4H), 7.07–7.39 (m,4H)

IR (KBr): 1743,1664 cm^{-1}

FAB-MS: 1037 $[M+H]^+$

EXAMPLE 16

n-Hexyl bromide (0.25 ml) was used instead of ethyl iodide. Except above matter,

MeLeu—D-p-HexOPhLac-MeLeu—D-Lac-MeLeu—D-p-HexOPhLac-MeLeu—D-Lac

(0,179 g) was obtained according to a similar manner to that of Example 15.

NMR ($CDCl_3$,δ): 0.70–1.9 (m,64H),2.68–3.2 (m,16H), 3.91 (t,4H),4.42–4.56 (m) and 5.03–5.9 (m) (8H),6.69–6.84 (m,4H),7.05–7.2 (m,4H)

IR (KBr): 1742,1661 cm^{-1}

FAB-MS: 1149 $[M+H]^+$

EXAMPLE 17

To Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (1.03 g) was added 4N-hydrogen chloride in ethyl acetate solution (20 ml), and stirred for 50 minutes at 0° C. After the solvent was evaporated in vacuo, the residue was azeotroped by toluene, was added dichloromethane (850 ml), cooled down to 0° C., added triethylamine (0.47 ml) and bis (2-oxo-3-oxazolidinyl) phosphinic chloride (0.32 g), and stirred for 14 hours successively. The solvent was evaporated in vacuo, was added 5% citric acid (100 ml) and extracted with ethyl acetate (100 ml×2). After washing the ethyl acetate layer with aqueous saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MEPhLac-MeLeu—D-Lac-MeLeu—D-p-MEPhLac-MeLeu—D-Lac

(0.506 g).

NMR ($CDCl_3$,δ): 0.78–1.08 (m,24H),1.2–1.9 (m,18H), 2.62–3.09 (m, 16H),3.45 (s,6H),3.65–3.82 (m,4H), 4.02–4.19 (m,4H),4.6–4.78 (m) and 5.01–5.7 (m) (8H), 6.8–6.96 (m,4H),7.12–7.22 (m,4H)

IR (KBr): 1740,1662 cm^{-1}

FAB-MS: 1097 $[M+H]^+$

EXAMPLE 18

A suspension of

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(0.3 g), dimethylformamide (2 ml), potassium carbonate (128.5 mg),1-bromo- 2-(2-methoxyethoxy)ethane (0.93 ml), and sodium iodide (92.9 mg) were stirred for 17 hours at room temperature and stirred for 24 hours at 50° C. Further, to the mixture was added sodium iodide (92.9 mg) and stirred for 8 hours successively. To the mixture was added water (30 ml) and extracted with ether (20 ml×3). After washing the ether layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography and eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (30:65:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MEEPhLac-MeLeu—D-Lac-MeLeu—D-p-MEEPhLac-MeLeu—D-Lac

(0.105 g).

NMR ($CDCl_3$,δ): 0.71–1.82 (m,54H),2.84–3.23 (m,16H), 3.39 (s,6H), 3.59–3.63 (m,4H),3.63–3.79 (m,4H),3.79–3.92 (m,4H),4.03–4.2 (m,4H), 4.39–4.56 (m) and 5.0–5.77 (m) (8H),6.83 (d,4H),7.13 (d,4H)

IR (KBr): 1743,1662 cm^{-1}

FAB-MS: 1185 $[M+H]^+$

EXAMPLE 19

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (1.24 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-o-MeOPhLac-MeLeu—D-Lac-MeLeu—D-o-MeOPhLac-MeLeu—D-Lac

(0.87 g) was obtained according to a similar manner to that of EXAMPLE 17.

NMR ($CDCl_3$,δ): 0.79–1.08 (m,24H),1.20–1.81 (m,18H), 2.71–3.15 (m, 16H),3.85 (s) and 3.86 (s) (6H),4.40–5.89 (m,8H),6.82–6.93 (m,4H),7.12–7.27 (m,4H)

IR (KBr):**1741,1663**cm^{-1}

FAB-MS: 1009 $[M+H]^+$

EXAMPLE 22

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D- 2,4-DMOPhLac-MeLeu-D-Lac-OH (1.49 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-2,4-DMOPhLac-MeLeu—D-Lac-MeLeu—D-2,4-DMO—PhLac-MeLeu—D-Lac

EXAMPLE 20

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.79 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-m-MeOPhLac-MeLeu—D-Lac-MeLeu—D-m-MeOPhLac-MeLeu—D-Lac

(0.51 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.75–1.15 (m,24H),1.20–1.85 (m,18H), 2.70–3.18 (m, 16H),3.78 (s,6H),4.40–5.78 (m,8H), 6.70–6.88 (m,6H),7.10–7.25 (m,2H)

IR (KBr):**1739,1661**cm^{-1}

FAB-MS: 1009M+H]$^+$

EXAMPLE 21

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D- 3,4-DMOPhLac-MeLeu-D-Lac-OH (0.26 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-3,4-DMOPhLac-MeLeu—D-Lac-MeLeu—D-3,4-DMO—PhLac-MeLeu—D-Lac

(0.14 g) was obtained according to a similar manner to that of EXAMPLE 17.

NMR ($CDCl_3$,δ): 0.72–1.00 (m,24H),1.21–1.80 (m,18H), 2.72–3.15 (m, 16H),3.85 (s,6H),3.86 (s,6H),4.42–5.72 (m,8H),6.72–6.81 (m,6H)

IR (KBr): 1740,1661 cm^{-1}

FAB-MS: 1069 $[M+H]^+$

(0.95 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.78–1.12 (m,24H),1.20–1.80 (m,18H), 2.70–3.16 (m, 16H),3.75–3.90 (m,12H),4.40–5.83 (m,8H), 6.35–6.43 (m,4H),7.01–7.12 (m,2H)

IR (KBr): 1740,1661 cm^{-1}

FAB-MS: 1069 $[M+H]^+$

EXAMPLE 23

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.59 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-3,4-MODPhLac-MeLeu—D-Lac-MeLeu—D-3,4-MODPhLac-MeLeu—D-Lac

(0.29 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.80–1.12 (m,24H),1.22–2.00 (m,18H), 2.63–3.20 (m, 16H),4.35–4.53 (m) and 5.00–5.70 (m) (8H), 5.82–6.00 (m,4H),6.60–6.82 (m,6H)

IR (KBr):1740,1661 cm^{-1}
FAB-MS: 1037 $[M+H]^+$

EXAMPLE 24

3HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D- 3MA-4MOPhLac-MeLeu-D-Lac-OH (1.18 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-3MA-4MOPhLac-MeLeu—D-Lac-MeLeu—D-3MA-4MOPhLac-MeLeu—D-Lac

(0.390 g) was obtained according to a similar manner to that of Example 5.
NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.2–2.1 (m,18H), 2.6–3.3 (m,28H), 3.85 (s,6H),4.4–4.55 (m) and 5.0–5.7 (m) (8H),67–6.9 (m,6H)
IR (KBr):1741,1663 cm^{-1}
FAB-MS: 1095 $[M+H]^+$

EXAMPLE 25

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D- 3,4-DMAPhLac-MeLeu-D-Lac-OH (0.35 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH, and N-methylmorpholine (0.186 ml) was used instead of triethylamine. Except above matter,

MeLeu—D-3,4-DMAPhLac-MeLeu—D-Lac-MeLeu—D-3,4-DMAPhLac-MeLeu—D-Lac

(0.19 g) was obtained according to a similar manner to that of Example 17.
NMR ($CDCl_3$,δ): 0.70–1.10 (m,24H),1.15–1.90 (m,18H), 2.68–3.20 (m,40H),4.39–4.60 (m) and 4.95–5.75 (m) (8H), 6.65–6.80 (m,6H)
IR (KBr):1739,1662 cm^{-1}
FAB-MS: 1121 $[M+H]^+$

EXAMPLE 26

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.82 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-o-FPhLac-MeLeu—D-Lac-MeLeu—D-o-FPhLac-MeLeu—D-Lac

(0.58 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.64–1.13 (m,24H),1.21–1.83 (m,18H), 2.63–3.22 (m,16H),4.4–4.57 (m) and 5.02–5.82 (m) (8H), 6.98–7.38 (m,8H)

IR (KBr): 1743,1663 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 27

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.77 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-m-FPhLac-MeLeu—D-Lac-MeLeu—D-m-FPhLac-MeLeu—D-Lac

(0.534 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.7–1.06 (m,24H),1.1–1.95 (m,18H), 2.6–3.27 (m,16H),4.4–4.58 (m) and 5.0–5.78 (m) (8H), 6.82–7.1 (m,6H),7.18–7.38 (m,2H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 28

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.99 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-FPhLac-MeLeu—D-Lac-MeLeu—D-p-FPhLac-MeLeu—D-Lac

(0.686 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.7–1.1 (m,24H),1.18–1.9 (m,18H), 2.62–3.23 (m,16H),4.4–4.58 (m) and 5.0–5.75 (m) (8H), 6.89–7.07 (m,4H),7.07–7.25 (m,4H)

IR (KBr): 1741,1662 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 29

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-MeOPhLac-MeLeu—D-Lac-MeLeu—D-PhLac-MeLeu—D-Lac

(0.461 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.78–1.06 (m,24H),1.3–1.82 (m,18H), 2.64–3.21 (m,16H),3.78 (s,3H),4.6–4.78 (m) and 5.02–5.8 (m) (8H),6.78–6.93 (m,2H),7.1–7.4 (m,7H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 979 $[M+H]^+$

EXAMPLE 30

HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.52 g) was used instead of HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-MeOPhLac-MeLeu-Glycol-MeLeu—D-MeOPhLac- MeLeu-Glycol

(0.26 g) was obtained according to a similar manner to that of Example 5.

NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.2–1.8 (m,12H), 2.7–3.2 (m,16H), 3.78 (s,3H),3.79 (s,3H),42–5.8 (m,10H), 6.75–6.9 (m,4H),7.05–7.2 (m,4H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 981 $[M+H]^+$

EXAMPLE 31

To an aqueous suspension (5 ml) of oxydiacetaldehyde bis(diethylacetal) (0.50 g) was added five drops of acetic acid and heated for half an hour at 100° C. To the resultant oxydiacetaldehyde solution was added acetonitrile solution (5 ml) of

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(0.198 g) and after stirring for half an hour at room temperature, adjusted to pH7.0 by aqueous saturated sodium bicarbonate solution. To the mixture was added sodium cyanoborohydride (0.055 g) and pH was kept under 7.5 with acetic acid and in the meanwhile, it was stirred for 2 hours at room temperature. To the resultant reaction solution was added water (50 ml) and aqueous saturated sodium bicarbonate solution (5 ml), and extracted with ethyl acetate. After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate, and ethanol (55:40:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MorPhLac-MeLeu—D-Lac-MeLeu—D-p-MorPhLac-MeLeu—D-Lac

(0.045 g).

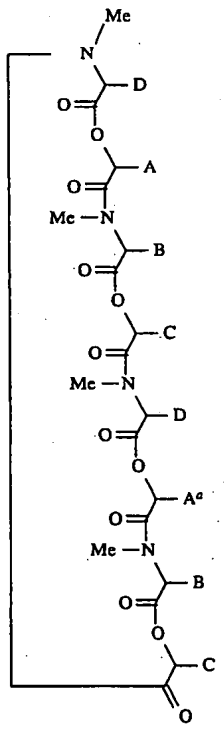
NMR ($CDCl_3$,δ): 0.8–1.1 (m,24H),1.3–1.8 (m,18H), 2.7–3.2 (m,24H), 3.8–3.9 (m,8H),4.4–4.55 (m) and 5.0–5.7 (m) (8H),6.82 (d,4H),7.13 (d, 4H)

IR (KBr): 1740,1662 cm^{-1}

FAB-MS: 1119 $[M+H]^+$

What we claim is:

1. A compound of the general formula (I):



(I)

wherein

A is a substituted benzyl group or a phenyl group which may have substituent(s),

A^a is a benzyl group which may have substituent(s) or a phenyl group which may have substituent(s),

B and D are each lower alkyl, and

C is hydrogen or lower alkyl,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by cyclic amino, dilower alkylamino or lower alkoxy,

B and D are each isopropyl, and

C is methyl.

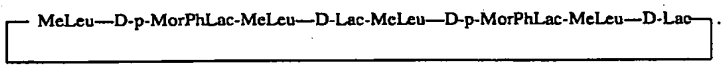
3. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by morpholino, dimethylamino or methoxy.

4. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by amino, nitro or hydroxy,

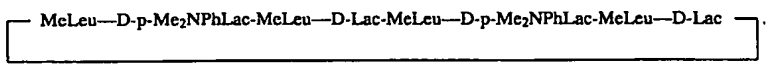
B and D are each isopropyl, and

C is methyl.

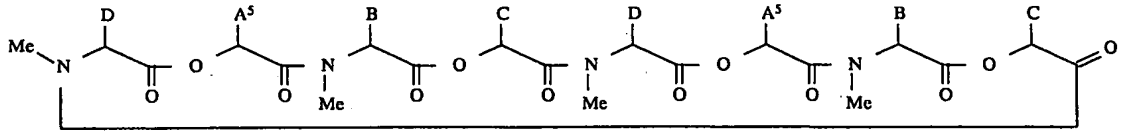
5. A compound of the formula:



6. A compound of the formula:

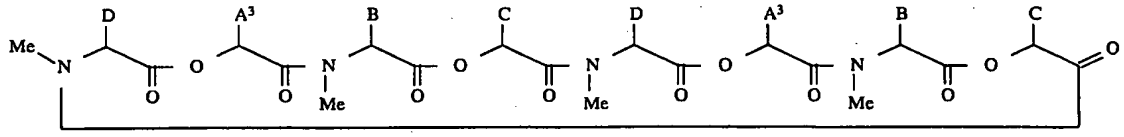


7. A process for preparation of a compound of the general formula:



or a salt thereof, which comprises

subjecting a compound of the general formula:



or a salt thereof, to a monoalkylation reaction followed by an intramolecular reaction,

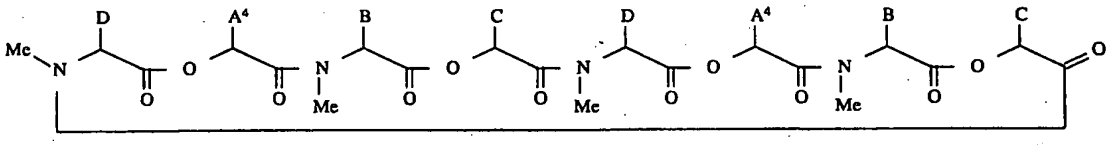
wherein B and D are each lower alkyl,

C is hydrogen or lower alkyl,

A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and

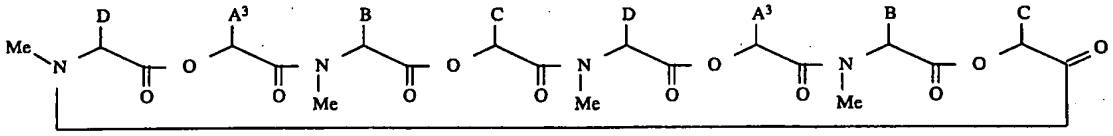
A^5 is a benzyl group substituted by cyclic amino, or a benzyl group substituted by cyclic amino and lower alkoxy.

8. A process for preparation of a compound of the general formula:



or a salt thereof, which comprises

subjecting a compound of the general formula:



or a salt thereof, to an alkylation reaction,

wherein B and D are each lower alkyl,

C is hydrogen or lower alkyl,

A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and

A^4 is a benzyl group substituted by mono- or di-lower alkylamino, or a benzyl group substituted by mono- or di-lower alkylamino and lower alkoxy.

9. An anthelmintic agent which comprises a compound or a pharmaceutically acceptable salt thereof of claim **1** as an active ingredient.

10. The compound of claim **1** wherein B and D are each an isobutyl group.

11. The compound of claim **1** wherein A and A^a are each a benzyl group substituted by a para-methoxy group.

12. The process of claim **7** wherein B and D are each an isobutyl group.

* * * * *

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUST
1940 DUKE STREET
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,514,773	**$940.00**	**$0.00**	**11/01/99**	**08/295,782**	**05/07/96**	**09/12/94**	**04**	**NO**	**188590PCT**

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DEPSIPEPTIDE DERIVATIVE, PRODUCTION THEREOF AND USE THEREOF

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☐ was filed as PCT international application

Number PCT/JP93/00286

on March 8, 1993,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under Section 119 of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year	Priority Claimed
4-92070	Japan	17/03/92	☑ Yes ☐ No
4-305093	Japan	15/10/92	☑ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, We (I) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number, 25,599; Arthur I. Neustadt, Registration Number 24,854; Robert C. Miller, Registration Number 25,357; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number, 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Stuart D. Dwork, Registration Number 31,103; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; William B. Walker, Registration Number 22,498; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Gilberto M. Villacorta, Registration Number 34,038; and John H.O. Clarke, Registration Number 17,373; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Hitoshi Nishiyama
NAME OF FIRST ~~SOLE~~ INVENTOR

Residence: 13-1-317, Kuzuharashinmachi, Neyagawa-shi, OSAKA 572 JAPAN
JPX

Hitoshi Nishiyama
Signature of Inventor

Citizen of: Japan

Post Office Address: the same as above

August 5, 1994
Date

2-00

Masaru Ohgaki
NAME OF SECOND JOINT INVENTOR

Masaru Ohgaki
Signature of Inventor

August 5, 1994
Date

Residence: 3-1-58-317, Minatojimanakamachi, Chuo-ku, Kobe-shi, HYOGO 572 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

3-00

~~Ryo~~ Yamanishi
NAME OF THIRD JOINT INVENTOR

Ryo Yamanishi
Signature of Inventor

August 5, 1994
Date

Residence: 16-3, Hoshimi-cho, Ibaraki-shi, OSAKA 567 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

4-00

Toshihiko Hara
NAME OF FOURTH JOINT INVENTOR

Toshihiko Hara
Signature of Inventor

August 5, 1994
Date

Residence: 565-19, Ooaza Miyaji, Miura-mura, Inashiki-gun, IBARAKI 300-04 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

STATEMENT

Assistant Commissioner for Patents
Alexandria, VA 22313-1450

Sir/Madam:

I, Katsunobu Ihara, of which postal address is ARK MORI BLDG, 13F, 12-32, Akasaka 1-chome, Minato-ku, Tokyo, Japan hereby state that:

I well understand the Japanese and English languages and attached is an accurate English translation made by me of the certified copy of the commercial register (Certificate of All the Records Registered) of Astellas Pharma Inc.

Date : July 1, 2005 Name : 井原 克誠

Katsunobu IHARA

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

Certificate of All the Records Registered

Trade name	Yamanouchi Pharmaceutical Co., Ltd.	
	Astellas Pharma Inc.	Changed April 1, 2005 Registered April 1, 2005
Location of head office	3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
Method of public notice	The statement is executed by publication in the *Nihon Keizai Shimbun* issued in Tokyo.	
Matters necessary for obtaining information relating to the balance sheet	http://www.yamanouchi.com/jp/index.html	Established March 25, 2003 Registered April 1, 2003
	http://www.astellas.com/jp	Changed April 1, 2005 Registered April 1, 2005
Date of incorporation	March 20, 1939	
Object	1. Manufacture, sale, import and export of pharmaceuticals, quasi-drugs, drugs used for animals, industrial chemicals, agricultural chemicals and other chemical products 2. Manufacture, sale, import and export of foods, food additives, seasonings, livestock feeds, feed additives, cosmetics, sanitary fixtures, medical instruments, meters and gauges, daily necessaries and miscellaneous goods 3. Manufacture, sale, import and export of medical machines and equipment, industrial machines and equipment and household equipment 4. Manufacture, sale, import and export of alcoholic beverages and other beverages 5. Breeding, sale, import and export of laboratory animals 6. Sale, purchase, lease, and management of real estate and agency business thereof 7. Warehouse business and road transport business 8. Hotel business, and management and control of health and physical education facilities and equipment 9. Casualty insurance agency business 10. Information processing service business using computer 11. All businesses incidental to or related to one of the preceding Items	
	1. Manufacture, sale, import and export of pharmaceuticals, quasi-drugs, drugs used for animals, reagents, industrial chemicals, agricultural chemicals and other chemical products 2. Manufacture, sale, import and export of foods, food additives, seasonings, fertilizers, livestock feeds, feed additives, cosmetics, sanitary fixtures, medical instruments, medical instruments used for animals, meters and gauges, daily necessaries and miscellaneous goods 3. Sale, purchase, import and export of natural products 4. Lease and maintenance of medical instruments 5. Manufacture, sale, import, export, lease and maintenance of medical machines and equipment, industrial machines and equipment and household equipment 6. Scientific inspections related to medical treatment 7. Manufacture, sale, import and export of liquors, alcoholic beverages and other beverages 8. Breeding, sale, import and export of laboratory animals 9. Sale, purchase, lease, and management of real estate and agency business thereof 10. Warehouse business, road transport business and freight transport business	

*Underlined letters are underlined

	11. Hotel business, and management and control of health and physical education facilities and equipment 12. Casualty insurance agency business 13. Publishing business 14. Sale, lease and maintenance of computer 15. Development, sale and lease of computer software 16. Information processing and information service business using computer 17. Management consulting business 18. All businesses incidental to or related to one of the preceding Items Changed April 1, 2005, and registered April 1, 2005	
Number of shares of one unit	1,000 shares	
	100 shares	Changed April 1, 2002 Registered April 2, 2002
Total number of shares authorized to be issued	800 million shares	
	2 billion shares	 Registered April 1, 2005
Total number of shares issued giving type of stock and number of shares of each type	Total number of issued shares 361,152,522 shares	Changed April 30, 2001 Registered May 9, 2001
	Total number of issued shares 361,203,052 shares	Changed February 28, 2002 Registered March 11, 2002
	Total number of issued shares 361,203,604 shares	Changed April 30, 2002 Registered May 10, 2002
	Total number of issued shares 361,214,262 shares	Changed May 31, 2002 Registered June 12, 2002
	Total number of issued shares 361,216,470 shares	Changed December 30, 2002 Registered January 14, 2003
	Total number of issued shares 361,221,523 shares	Changed April 30, 2004 Registered May 13, 2004
	Total number of issued shares 361,549,971 shares	Changed October 31, 2004 Registered November 10, 2004
	Total number of issued shares 361,954,215 shares	Changed January 31, 2005 Registered February 8, 2005
	Total number of issued shares 571,428,003 shares	 Registered April 1, 2005
Amount of capital	¥99,694,563,841	Changed April 30, 2001 Registered May 9, 2001
	¥99,744,563,841	Changed February 28, 2002 Registered March 11, 2002
	¥99,745,563,513	Changed April 30, 2002 Registered May 10, 2002
	¥99,756,563,185	Changed May 31, 2002 Registered June 12, 2002
	¥99,760,561,873	Changed December 30, 2002 Registered January 14, 2003
	¥99,765,561,873	Changed April 30, 2004 Registered May 13, 2004
	¥100,090,561,873	Changed October 31, 2004 Registered November 10, 2004
	¥100,490,561,873	Changed January 31, 2005 Registered February 8, 2005

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

Name, address, and place of business of transfer agent	33-1, Shiba 3-chome, Minato-ku, Tokyo The Chuo Mitsui Trust and Banking Company, Limited 33-1, Shiba 3-chome, Minato-ku, Tokyo Head Office, The Chuo Mitsui Trust and Banking Company, Limited Changed December 4, 2000, and registered December 8, 2000	
Matters relating to officers	Director Masayoshi Onoda	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Toichi Takenaka Director Toichi Takenaka	Reappointed June 28, 2001 Registered July 10, 2001 Reappointed June 27, 2003 Registered July 11, 2003 Resigned March 31, 2005 Registered April 1, 2005
	Director Kaoru Kimura	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Munetoshi Kakitani	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Nobuji Takayama Director Nobuji Takayama	Reappointed June 28, 2001 Registered July 10, 2001 Reappointed June 27, 2003 Registered July 11, 2003 Resigned March 31, 2005 Registered April 1, 2005
	Director Kiyoshi Kawaishi	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Hidehiko Ueda Director Hidehiko Ueda	Reappointed June 29, 2000 Registered July 12, 2000 Reappointed June 27, 2002 Registered July 10, 2002 Retired June 24, 2004 Registered July 7, 2004
	Director Hiroshi Suzuki	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Youzou Noura	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Masakatsu Inoue	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002

*Dates are underlined

	Director Toshinari Tamura	Reappointed June 29, 2000
		Registered July 12, 2000
	Director Toshinari Tamura	Reappointed June 27, 2002
		Registered July 10, 2002
	Director Toshinari Tamura	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Director Kunihide Ichikawa	Reappointed June 29, 2000
		Registered July 12, 2000
	Director Kunihide Ichikawa	Reappointed June 27, 2002
		Registered July 10, 2002
	Director Kunihide Ichikawa	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Director Shigekazu Takahashi	Reappointed June 28, 2001
		Registered July 10, 2001
	Director Shigekazu Takahashi	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Kazuyoshi Hatanaka	Appointed June 29, 2000
		Registered July 12, 2000
	Director Kazuyoshi Hatanaka	Reappointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Yasuo Ishii	Appointed June 29, 2000
		Registered July 12, 2000
	Director Yasuo Ishii	Reappointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Toshio Saba	Appointed June 28, 2001
		Registered July 10, 2001
	Director Toshio Saba	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Isao Kishi	Appointed June 28, 2001
		Registered July 10, 2001
	Director Isao Kishi	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Hiroaki Hiraiwa	Appointed June 28, 2001
		Registered July 10, 2001
	Director Hiroaki Hiraiwa	Reappointed June 27, 2003
		Registered July 11, 2003

	Resigned June 24, 2004
	Registered July 7, 2004
Director Isao Yanagisawa	Appointed June 28, 2001
	Registered July 10, 2001
Director Isao Yanagisawa	Reappointed June 27, 2003
	Registered July 11, 2003
Director Isao Yanagisawa	Family name of Isao Yanagisawa
	Modified March 19, 2004
	Resigned June 24, 2004
	Registered July 7, 2004
Director Shinji Usuda	Appointed June 27, 2002
	Registered July 10, 2002
	Retired June 24, 2004
	Registered July 7, 2004
Director Ikuya Sugisaki	Appointed June 27, 2002
	Registered July 10, 2002
	Retired June 24, 2004
	Registered July 7, 2004
Director Hajime Nakajima	Appointed June 27, 2002
	Registered July 10, 2002
	Retired June 24, 2004
	Registered July 7, 2004
Director Iwaki Miyazaki	Appointed June 27, 2003
	Registered July 11, 2003
	Resigned June 24, 2004
	Registered July 7, 2004
Director Kouji Yoshinaga	Appointed June 27, 2003
	Registered July 11, 2003
	Resigned June 24, 2004
	Registered July 7, 2004
Director Tadao Hasegawa	Appointed June 27, 2003
	Registered July 11, 2003
	Resigned June 24, 2004
	Registered July 7, 2004
Director Makoto Matsuo (is an outside director)	Appointed June 24, 2004
	Registered July 7, 2004
	Resigned March 31, 2005
	Registered April 1, 2005
Director Hatsuo Aoki	Appointed April 1, 2005
	Registered April 1, 2005
Director Toichi Takenaka	Appointed April 1, 2005
	Registered April 1, 2005
Director Toshinari Tamura	Appointed April 1, 2005
	Registered April 1, 2005
Director Masafumi Nogimori	Appointed April 1, 2005
	Registered April 1, 2005
Director Kunihide Ichikawa	Appointed April 1, 2005
	Registered April 1, 2005
Director Koichi Sejima	Appointed April 1, 2005
	Registered April 1, 2005

*Underlined items are underlined

	Director Akiro Kojima (is an outside director)	Appointed April 1, 2005
		Registered April 1, 2005
	Director Makoto Matsuo (is an outside director)	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Masayoshi Onoda 931-35, Nonoshita 3-chome, Nagareyama-shi, Chiba	Reappointed June 28, 2001
		Registered July 10, 2001
		Resigned June 27, 2002
		Registered July 10, 2002
	Representative Director Toichi Takenaka 505-56, Matsugaoka 4-chome, Nagareyama-chi, Chiba	Reappointed June 28, 2001
		Registered July 10, 2001
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Changed address March 10, 2003
		Registered March 17, 2003
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Reappointed June 27, 2003
		Registered July 11, 2003
		Retired March 31, 2005
		Registered April 1, 2005
	Representative Director Hidehiko Ueda 3-2-1202, Nihonbashi Hamacho 2-chome, Chuo-ku, Tokyo	Appointed June 27, 2003
		Registered July 11, 2003
		Retired June 24, 2004
		Registered July 7, 2004
	Representative Director Toshinari Tamura 21-10, Midoricho 1-chome, Hasuda-shi, Saitama	Appointed October 1, 2004
		Registered October 1, 2004
		Retired March 31, 2005
		Registered April 1, 2005
	Representative Director Hatsuo Aoki 13-3, Hata 4-chome, Ikeda-shi, Osaka	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Toshinari Tamura 21-10, Midoricho 1-chome, Hasuda-shi, Saitama	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Masafumi Nogimori 65-2, Makamicho 6-chome, Takatsuki-shi, Osaka	Appointed April 1, 2005
		Registered April 1, 2005
	Auditor Hiroyuki Himaki	Appointed June 29, 2000
		Registered July 12, 2000
		Retired June 27, 2003
		Registered July 11, 2003
	Auditor Norio Sasaki	Appointed June 29, 2000
		Registered July 12, 2000
	Auditor Norio Sasaki	Reappointed June 27, 2003

		Registered July 11, 2003
		Retired March 31, 2005
		Registered April 1, 2005
	Auditor Shirou Tachikawa	Appointed June 29, 2000
		Registered July 12, 2000
		Retired June 27, 2003
		Registered July 11, 2003
	Auditor Toyomichi Ohtani	Appointed June 28, 2001
		Registered July 10, 2001
	Auditor Toyomichi Ohtani	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Auditor Hideo Yamada	Appointed June 28, 2001
		Registered July 10, 2001
	Auditor Hideo Yamada	Reappointed June 24, 2004
		Registered July 7, 2004
	Auditor Kenichirou Saitou	Appointed June 27, 2003
		Registered July 11, 2003
	Auditor Makoto Matsuo	Appointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Auditor Masaya Ishii	Appointed April 1, 2005
		Registered April 1, 2005
	Auditor Kanji Kobayashi	Appointed April 1, 2005
		Registered April 1, 2005
Branch office	1 4-7, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-7, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	Moved September 28, 2002
		Registered October 4, 2002
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 24, 2005
		Registered February 1, 2005
	2 7-12, Kitahama 3-chome, Chuo-ku, Osaka	
	6-5, Kawaramachi 3-chome, Chuo-ku, Osaka	Moved May 19, 2003
		Registered May 21, 2003
	3 9-1, Oodori-nishi 5-chome, Chuo-ku, Sapporo, Hokkaido	
	4 10-21, Sakae 1-chome, Naka-ku, Nagoya	
	1-36, Marunouchi 2-chome, Naka-ku, Nagoya	Moved April 1, 2005
		Registered April 1, 2005

*Underlined letters are underlined

	5 2-25, Oomachi 2-chome, Aoba-ku, Sendai, Miyagi	
	6 18-25, Hakataeki-higashi 1-chome, Hakata-ku, Fukuoka	
	2-1, Shimokawabata, Hakata-ku, Fukuoka	Moved April 1, 2005 Registered April 1, 2005
	7 5-6, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 31, 2005 Registered February 1, 2005
	24-8, Higashiueno 5-chome, Taito-ku, Tokyo	Moved April 1, 2005 Registered April 1, 2005
	8 4-8, Kotobukicho 1-chome, Takamatsu-shi, Kagawa	
	2-1, Sunport, Takamatsu-shi, Kagawa	Moved March 22, 2004 Registered March 22, 2004
	9 7-2, Otemachi 3-chome, Naka-ku, Hiroshima	
	11-10, Otemachi 2-chome, Naka-ku, Hiroshima	Moved April 1, 2005 Registered April 1, 2005
	10 287, Nanjing Donglu 3-duan, Taibei	
		Abolished October 31, 2004 Registered November 1, 2004
	11 84-2, Ohtamachi 6-chome, Naka-ku, Yokohama	
	2-1, Minatomirai 2-chome, Nishi-ku, Yokohama	Moved February 25 2003 Registered March 4, 2003
	12 513, Akinono-cho, Nijo-sagaru, Karasuma-dori, Nakagyo-ku, Kyoto	
	13 5-6, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 31, 2005 Registered February 1, 2005
	7-5, Sakuragicho 1-chome, Omiya-ku, Saitama	Moved April 1, 2005 Registered April 1, 2005

	15 2-25, Oomachi 2-chome, Aoba-ku, Sendai, Miyagi	Established April 1, 2005 Registered April 1, 2005
	16 24-8, Higashiueno 5-chome, Taito-ku, Tokyo	Established April 1, 2005 Registered April 1, 2005
	17 6, Nakase 2-chome, Mihama-ku, Chiba	Established April 1, 2005 Registered April 1, 2005
	18 5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Established April 1, 2005 Registered April 1, 2005
	19 1-36, Marunouchi 2-chome, Naka-ku, Nagoya	Established April 1, 2005 Registered April 1, 2005
	20 5-2, Hon-machi 1-chome, Kanazawa-shi, Ishikawa	Established April 1, 2005 Registered April 1, 2005
	21 6-5, Kawaramachi 3-chome, Chuo-ku, Osaka	Established April 1, 2005 Registered April 1, 2005
	22 1-7, Isobedori 3-chome, Chuo-ku, Kobe	Established April 1, 2005 Registered April 1, 2005
	23 1-3, Shimo-ishii 1-chome, Okayama	Established April 1, 2005 Registered April 1, 2005
	24 2-1, Shimokawabata, Hakata-ku, Fukuoka	Established April 1, 2005 Registered April 1, 2005
Equity warrant	First equity warrant Number of equity warrants: 1,410 Type and number of shares for equity warrants Common shares of the Company: 141,000 shares The number of shares of stock for one equity warrant (hereinafter referred to as the "number of granted shares") shall be 100 shares. In the event of a stock split or reverse stock split involving the common shares of stock of the Company, the number of granted shares shall be adjusted based on the following formula. Any fractional number of shares less than one share that will arise as a result of the adjustment shall be discarded. Number of granted shares after adjustment = number of granted shares before adjustment x ratio of stock split or reverse stock split When there is an unavoidable reason requiring the adjustment of the number of granted shares such as capital decrease, merger or company spin-off of the Company, the number of granted shares shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Issue price of one equity warrant Free Amount of money to be paid at the time of the exercise of each equity warrant The amount of money to be paid at the time of the exercise of each equity warrant shall be the amount obtained by multiplying the number	

of granted shares by the amount of money to be paid for one share to be issued or transferred through the exercise of each equity warrant (hereinafter referred to as the "exercise price").
The exercise price shall be the average of the closing prices (hereinafter referred to as the "closing price") of ordinary transactions of the Company's common shares at the Tokyo Stock Exchange for the days (excluding days when no transactions were carried out) of the month preceding the month that includes the date of issue of equity warrants (hereinafter referred to as the "issuing date"). Any fractional number of less than one yen shall be rounded up to one yen. However, if the exercise price is lower than the closing price on the issuing date (if there was no closing price on the issuing date, it shall be the closing price on the immediately preceding date), the said closing price shall become the exercise price.
When the Company issues new common shares or disposes of treasury stock at a price lower than market price (with the exception of the exercise of equity warrants and the conversion of convertible bonds based on the Commercial Code before the enforcement of the Law for Partial Amendment of the Commercial Code, etc. (No. 128 law of 2001)), the exercise price shall be adjusted based on the following formula. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.

Exercise price after adjustment = exercise price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares)

The "number of already issued shares" used for the above formula shall be the number of shares obtained by deducting the number of treasury stock held by the Company from the number of outstanding shares of the Company. When treasury stock is disposed of, the "number of newly issued shares" shall be read as the "number of disposed treasury shares."
In the event of a stock split or reverse stock split of the common shares of the Company on or after the issuing date, the exercise price shall be adjusted proportionately based on the ratio of the stock split or reverse stock split. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.
When there is an unavoidable reason requiring the adjustment of the exercise price such as capital decrease, merger or company spin-off of the Company on and after the issuing date, the exercise price shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc.
Period for the exercise of equity warrants:
From July 1, 2005 to June 27, 2013
Conditions for the exercise of equity warrants (excluding the amount of payment and period for exercise):
The partial exercise of each equity warrant shall not be allowed.
Reasons for the Company's cancellation of equity warrants and conditions for cancellation:
(i) When a proposal for the approval of a merger agreement under which the Company will not be the surviving company is approved at the general shareholders meeting of the Company, or a proposal for the approval of a stock exchange agreement or stock transfer based on which the Company will become a wholly-owned subsidiary is approved at the general shareholders meeting of the Company, the Company may cancel the equity warrants without

	consideration. (ii) The Company may cancel without consideration equity warrants acquired and held by the Company which were not yet exercised. Registered July 11, 2003
	Second equity warrant Number of equity warrants: 1,470 Type and number of shares for equity warrants Common shares of the Company: 147,000 shares The number of shares of stock for one equity warrant (hereinafter referred to as the "number of granted shares") shall be 100 shares. In the event of a stock split or reverse stock split involving the common shares of stock of the Company, the number of granted shares shall be adjusted based on the following formula. Any fractional number of shares less than one share that will arise as a result of the adjustment shall be discarded. Number of granted shares after adjustment = number of granted shares before adjustment x ratio of stock split or reverse stock split When there is an unavoidable reason requiring the adjustment of the number of granted shares such as capital decrease, merger or company spin-off of the Company, the number of granted shares shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Issue price of one equity warrant Free Amount of money to be paid at the time of the exercise of each equity warrant The amount of money to be paid at the time of the exercise of each equity warrant shall be the amount obtained by multiplying the number of granted shares by the amount of money to be paid for one share to be issued or transferred through the exercise of each equity warrant (hereinafter referred to as the "exercise price"). The exercise price shall be the average of the closing prices (hereinafter referred to as the "closing price") of ordinary transactions of the Company's common shares at the Tokyo Stock Exchange for the days (excluding days when no transactions were carried out) of the month preceding the month that includes the date of issue of equity warrants (hereinafter referred to as the "issuing date"). Any fractional number of less than one yen shall be rounded up to one yen. However, if the exercise price is lower than the closing price on the issuing date (if there was no closing price on the issuing date, it shall be the closing price on the immediately preceding date), the said closing price shall become the exercise price. When the Company issues new common shares or disposes of common treasury stock at a price lower than the market price on or after the issuing date (with the exception of the exercise of equity warrants, the conversion of convertible bonds based on the Commercial Code before the enforcement of the Law for Partial Amendment of the Commercial Code, etc. (No. 128 law of 2001) and the transfer of treasury stock based on the provision of Article 221-2 (request for sale of shares that are less than the number of shares in one stock trade unit) of the Commercial Code), the exercise price shall be adjusted based on the following formula. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.

	Exercise price after adjustment = exercise price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The "number of already issued shares" used for the above formula shall be the number of shares obtained by deducting the number of treasury stock held by the Company from the number of outstanding shares of the Company. When treasury stock is disposed of, the "number of newly issued shares" shall be read as the "number of disposed treasury shares." In the event of a stock split or reverse stock split of the common shares of the Company on or after the issuing date, the exercise price shall be adjusted proportionately based on the ratio of the stock split or reverse stock split. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen. When there is an unavoidable reason requiring the adjustment of the exercise price such as capital decrease, merger or company spin-off of the Company on and after the issuing date, the exercise price shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Period for the exercise of equity warrants: From July 1, 2006 to June 24, 2014 Conditions for the exercise of equity warrants (excluding the amount of payment and period for exercise): The partial exercise of each equity warrant shall not be allowed. Reasons for the Company's cancellation of equity warrants and conditions for cancellation: (i) When a proposal for the approval of a merger agreement under which the Company will not be the surviving company is approved at the general shareholders meeting of the Company, or a proposal for the approval of a stock exchange agreement or stock transfer based on which the Company will become a wholly-owned subsidiary is approved at the general shareholders meeting of the Company, the Company may cancel the equity warrants without consideration. (ii) The Company may cancel without consideration equity warrants acquired and held by the Company which were not yet exercised. Registered July 7, 2004
Convertible corporate bond	Third unsecured convertible corporate bond Total amount of convertible bonds ¥14,921,000,000 ¥14,915,000,000 Changed April 30, 2001, and registered May 9, 2001 ¥14,913,000,000 Changed April 30, 2002, and registered May 10, 2002 ¥14,911,000,000 Changed May 31, 2002, and registered June 12, 2002 ¥14,903,000,000 Changed December 30, 2002, and registered January 14, 2003 Conditions for conversion: The issue price per share of the shares (the "conversion price") issued through conversion shall be decided as shown in (1) below, and the number of shares to be issued through conversion shall be as shown below. However, conversion shall not be requested for part of the face value of these bonds and interest.

*Underlined

	Number of shares = total of the face values of these bonds presented by each bond holder for the request of a conversion / conversion price In this event, if any fractional number of shares less than one share is created, the amount of the face value of bonds equivalent to the fractional number of shares shall be redeemed at a rate of 100 yen for the face value of 100 yen. (1) Conversion price: 4,413 yen (2) Adjustment of the conversion price If the company issues new shares at a paid amount which is lower than market price after the issue of these bonds, the conversion price shall be adjusted based on the following formula. Conversion price after adjustment = conversion price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The conversion price shall also be adjusted in the event of a stock dividend, free issue and stock split or reverse stock split. When, in the event of the issue of registered par value common shares of the company through conversion, the conversion price after adjustment is lower than the par value of the registered par value common shares of the company, the par value shall become the conversion price. Details of shares to be issued through conversion: Registered par value common shares of the company (par value per share: 50 yen) However, if the company decides that shares to be issued through the conversion of these bonds should be registered non-par-value common shares, the shares shall be registered non-par-value common shares of the company. Period for the request of conversion: From September 1, 1987 to December 30, 2002 Amount of each convertible bond: One million yen Amount of payment for each convertible bond: Full amount These bonds may be converted into shares.
	Expiration of the period for the request of conversion on December 30, 2002 Registered January 14, 2003
	Yen-denominated convertible bond to mature in 2014 Total amount of convertible bonds: ¥18,880,000,000 ¥18,680,000,000 Changed May 31, 1999, and registered June 14, 1999 ¥17,690,000,000 Changed June 30, 1999, and registered July 12, 1999 ¥11,230,000,000 Changed July 31, 1999, and registered August 10, 1999 ¥10,540,000,000 Changed August 31, 1999, and registered September 13, 1999 ¥9,650,000,000 Changed October 31, 1999, and registered November 12, 1999 ¥9,440,000,000 Changed November 30, 1999, and registered December 13, 1999 ¥9,220,000,000 Changed December 31, 1999, and registered January 14, 2000

	¥9,180,000,000 Changed January 31, 2000, and registered February 14, 2000 ¥8,390,000,000 Changed February 29, 2000, and registered March 14, 2000 ¥8,150,000,000 Changed April 30, 2000, and registered May 12, 2000 ¥8,140,000,000 Changed May 31, 2000, and registered June 13, 2000 ¥7,510,000,000 Changed July 31, 2000, and registered August 8, 2000 ¥7,290,000,000 Changed August 31, 2000, and registered September 11, 2000 ¥6,640,000,000 Changed November 30, 2000, and registered December 8, 2000 ¥6,610,000,000 Changed December 31, 2000, and registered January 12, 2001 ¥6,600,000,000 Changed January 31, 2001, and registered February 8, 2001 ¥6,500,000,000 Changed February 28, 2002, and registered March 11, 2002 ¥6,480,000,000 Changed May 31, 2002, and registered June 12, 2002 ¥6,470,000,000 Changed April 30, 2004, and registered May 13, 2004 ¥5,820,000,000 Changed October 31, 2004, and registered November 10, 2004 ¥5,020,000,000 Changed January 31, 2005, and registered February 8, 2005
	Conditions for conversion: These bonds may be converted into par value common shares of the Company at a rate of one par value common share of the Company for the following conversion price, based on the face amount of these bonds: However, any fractional number of shares less than one share created at the time of conversion shall be discarded, and no adjustment using cash shall be made. a. The initial conversion price shall be 1,979 yen per share. b. Revision of the conversion price When an amount obtained by multiplying the average closing price for 30 consecutive business days starting from 45 consecutive business days in which there is a closing price of ordinary transactions of the Company's par value common shares on the Tokyo Stock Exchange before March 31, 1998, March 31, 2004 and March 31, 2009, respectively, (hereinafter respectively referred to as the "determination date") by 1.025 (any fraction of less than one yen shall be rounded up to one yen) is lower by one yen or more than the conversion price effective on each determination date, on and after April 22, 1998, April 22, 2004, and April 22, 2009 (hereinafter respectively referred to as the "effective date"), respectively, the conversion price shall be changed to each amount calculated as above (subject, however, to the adjustment set out in c. below, which took effect between the determination date and a date prior to the effective date). However, as a result of the adjustment, the conversion price shall not be lowered to less than 50% of the initial conversion price (however, if adjusted as set out in c. below, it shall be the amount after adjustment). If the adjusted conversion price is less than 50% of the initial conversion price, the conversion price

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

	shall be the amount obtained by rounding up less than one yen of an amount equivalent to 50% of the conversion price to one yen. c. Adjustment of conversion price Where the Company issues new common shares at an amount for payment that is lower than the market price of the common shares of the Company after the issue of these bonds, the conversion price shall be adjusted based on the following formula: Conversion price after adjustment = conversion price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The conversion price shall be adjusted appropriately in the event of a stock split, reverse stock split, issue of convertible bonds or bonds with warrants at the initial conversion price, a warrant exercise price that is lower than the market price of the common shares of the Company, or in other certain cases; provided, however, that the conversion price shall not be lower than the par value of the common shares of the Company. Details of shares to be issued through conversion: Par value common shares of the Company (current par value per share: 50 yen) Period for request of conversion: From May 9, 1994 to close of business on March 24, 2014 (based on the time of a place where conversion is requested) Amount of each convertible bond: 10 million yen Amount of payment for each convertible bond: Full amount These bonds may be converted into shares.
Company spin-off	Spinning-off into Zepharma Inc. at 7-1, Nihonbashi-Honcho 2-chome, Chuo-ku Tokyo on October 1, 2004 Registered October 1, 2004
Merger	Merged Fujisawa Pharmaceutical Co., Ltd at 4-7, Doshomachi 3-chome, Chuo-ku Osaka Registered April 1, 2005
Matters concerning the registered record	Based on the provision of Paragraph 3 of the supplementary regulation of the 1989 Ministerial Ordinance No. 15 of the Ministry of Justice Transfered May 20, 1999

This is to certify that the above are all the matters that are recorded on the register that are not sealed.

April 7, 2005
Tokyo Legal Affairs Bureau
Registrar Motoyuki Ohba

履歴事項全部証明書

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

商　号	山之内製薬株式会社	
	アステラス製薬株式会社	平成１７年　４月　１日変更 平成１７年　４月　１日登記
本　店	東京都中央区日本橋本町二丁目３番１１号	
公告をする方法	東京都において発行する日本経済新聞に掲載する	
貸借対照表に係る情報の提供を受けるために必要な事項	ｈｔｔｐ：／／ｗｗｗ．ｙａｍａｎｏｕｃｈｉ．ｃｏｍ／ｊｐ／ｉｎｄｅｘ．ｈｔｍｌ	平成１５年　３月２５日設定 平成１５年　４月　１日登記
	ｈｔｔｐ：／／ｗｗｗ．ａｓｔｅｌｌａｓ．ｃｏｍ／ｊｐ	平成１７年　４月　１日変更 平成１７年　４月　１日登記
会社成立の年月日	昭和１４年３月２０日	
目　的	１．医薬品、医薬部外品、動物用医薬品、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、飼料および飼料添加物、化粧品、衛生用具、医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．医療用機械器具、産業用機械器具、家庭用機器の製造、販売および輸出入 ４．酒精飲料および飲料品の製造、販売および輸出入 ５．実験動物の飼育・販売および輸出入 ６．不動産の売買、賃貸借、管理およびその仲介 ７．倉庫業および道路運送事業 ８．旅館業および保健体育施設の経営および管理 ９．損害保険代理業 １０．コンピューターによる情報処理サービス業 １１．前各号に付帯または関連する一切の事業	
	１．医薬品、医薬部外品、動物用医薬品、試薬、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、肥料、飼料および飼料添加物、化粧品、衛生用具、医療用具、動物用医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．天産物の売買ならびに輸出入 ４．医療用具の賃貸借および保守 ５．医療用機械器具、産業用機械器具、家庭用機器の製造、販売、輸出入、賃貸借および保守	

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

	6．医療に関連する各種科学的検査 7．酒類、酒精飲料および飲料品の製造、販売および輸出入 8．実験動物の飼育・販売および輸出入 9．不動産の売買、賃貸借、管理およびその仲介 10．倉庫業、道路運送事業および貨物利用運送事業 11．旅館業および保健体育施設の経営および管理 12．損害保険代理業 13．出版業 14．コンピューターの販売、賃貸借および保守 15．コンピューターのソフトウェアの開発、販売および賃貸借 16．コンピューターによる情報処理・提供サービス業 17．経営コンサルタント業 18．前各号に付帯または関連する一切の事業 平成17年　4月　1日変更　　平成17年　4月　1日登記	
一単元の株式の数	1000株	
	100株	平成14年　4月　1日変更 平成14年　4月　2日登記
発行する株式の総数	8億株	
	20億株	平成17年　4月　1日登記
発行済株式の総数並びに種類及び数	発行済株式の総数 3億6115万2522株	平成13年　4月30日変更 平成13年　5月　9日登記
	発行済株式の総数 3億6120万3052株	平成14年　2月28日変更 平成14年　3月11日登記
	発行済株式の総数 3億6120万3604株	平成14年　4月30日変更 平成14年　5月10日登記
	発行済株式の総数 3億6121万4262株	平成14年　5月31日変更 平成14年　6月12日登記
	発行済株式の総数 3億6121万6470株	平成14年12月30日変更 平成15年　1月14日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	発行済株式の総数 ３億６１２２万１５２３株	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	発行済株式の総数 ３億６１５４万９９７１株	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	発行済株式の総数 ３億６１９５万４２１５株	平成１７年　１月３１日変更 平成１７年　２月　８日登記
	発行済株式の総数 ５億７１４２万８００３株	 平成１７年　４月　１日登記
資本の額	金９９６億９４５６万３８４１円	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	金９９７億４４５６万３８４１円	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	金９９７億４５５６万３５１３円	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	金９９７億５６５６万３１８５円	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	金９９７億６０５６万１８７３円	平成１４年１２月３０日変更 平成１５年　１月１４日登記
	金９９７億６５５６万１８７３円	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	金１０００億９０５６万１８７３円	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	金１００４億９０５６万１８７３円	平成１７年　１月３１日変更 平成１７年　２月　８日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

名義書換代理人の氏名及び住所並びに営業所	東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社 東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社　本店 平成１２年１２月　４日変更	平成１２年１２月　８日登記
役員に関する事項	取締役　小野田正愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　竹中登一	平成１３年　６月２８日重任 平成１３年　７月１０日登記
	取締役　竹中登一	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　木村薫	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　柿谷宗敏	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　髙　山　暢　二	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　髙　山　暢　二	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　河　石　清	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　上　田　英　彦	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　上　田　英　彦	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　鈴　木　弘	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　能　浦　栄　蔵	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　井上雅勝	平成１２年　６月２９日重任 平成１２年　７月１２日登記 平成１４年　６月２７日退任 平成１４年　７月１０日登記
	取締役　田村隼也 取締役　田村隼也 取締役　田村隼也	平成１２年　６月２９日重任 平成１２年　７月１２日登記 平成１４年　６月２７日重任 平成１４年　７月１０日登記 平成１６年　６月２４日重任 平成１６年　７月　７日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　市川邦英 取締役　市川邦英 取締役　市川邦英	平成１２年　６月２９日重任 平成１２年　７月１２日登記 平成１４年　６月２７日重任 平成１４年　７月１０日登記 平成１６年　６月２４日重任 平成１６年　７月　７日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　髙橋重一 取締役　髙橋重一	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　畑中和義	平成１２年　６月２９日就任 平成１２年　７月１２日登記
	取締役　畑中和義	平成１４年　６月２７日重任 平成１４年　７月１０日登記
		平成１６年　６月２４日退任 平成１６年　７月　７日登記
	取締役　石井康雄	平成１２年　６月２９日就任 平成１２年　７月１２日登記
	取締役　石井康雄	平成１４年　６月２７日重任 平成１４年　７月１０日登記
		平成１６年　６月２４日退任 平成１６年　７月　７日登記
	取締役　佐羽俊男	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	取締役　佐羽俊男	平成１５年　６月２７日重任 平成１５年　７月１１日登記
		平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　岸　功	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	取締役　岸　功	平成１５年　６月２７日重任 平成１５年　７月１１日登記
		平成１６年　６月２４日辞任 平成１６年　７月　７日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　平岩廣章	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　平岩廣章	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　柳沢勲	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　柳沢勲	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
	取締役　柳澤勲	柳沢勲の氏
		平成１６年　３月１９日更正
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　臼田眞治	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　杉崎生弥	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　中島一	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記

東京都中央区日本橋本町二丁目3番11号
アステラス製薬株式会社
会社法人等番号　0199－01－034966

取締役	宮崎石基	平成15年　6月27日就任 平成15年　7月11日登記 平成16年　6月24日辞任 平成16年　7月　7日登記
取締役	吉長孝三	平成15年　6月27日就任 平成15年　7月11日登記 平成16年　6月24日辞任 平成16年　7月　7日登記
取締役	長谷川忠夫	平成15年　6月27日就任 平成15年　7月11日登記 平成16年　6月24日辞任 平成16年　7月　7日登記
取締役 （社外取締役）	松尾眞	平成16年　6月24日就任 平成16年　7月　7日登記 平成17年　3月31日辞任 平成17年　4月　1日登記
取締役	青木初夫	平成17年　4月　1日就任 平成17年　4月　1日登記
取締役	竹中登一	平成17年　4月　1日就任 平成17年　4月　1日登記
取締役	田村隼也	平成17年　4月　1日就任 平成17年　4月　1日登記
取締役	野木森雅郁	平成17年　4月　1日就任 平成17年　4月　1日登記
取締役	市川邦英	平成17年　4月　1日就任 平成17年　4月　1日登記

整理番号　ク604523　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目3番11号
アステラス製薬株式会社
会社法人等番号　0199－01－034966

	取締役　瀬島宏一	平成17年　4月　1日就任 平成17年　4月　1日登記
	取締役　児島章郎 （社外取締役）	平成17年　4月　1日就任 平成17年　4月　1日登記
	取締役　松尾眞 （社外取締役）	平成17年　4月　1日就任 平成17年　4月　1日登記
	千葉県流山市野々下三丁目931番地の35 代表取締役　小野田正愛	平成13年　6月28日重任 平成13年　7月10日登記 平成14年　6月27日辞任 平成14年　7月10日登記
	千葉県流山市松ケ丘四丁目505番地の56 代表取締役　竹中登一	平成13年　6月28日重任 平成13年　7月10日登記
	東京都港区芝三丁目34番1－1405号 代表取締役　竹中登一	平成15年　3月10日住所移転 平成15年　3月17日登記
	東京都港区芝三丁目34番1－1405号 代表取締役　竹中登一	平成15年　6月27日重任 平成15年　7月11日登記 平成17年　3月31日退任 平成17年　4月　1日登記
	東京都中央区日本橋浜町二丁目3番2－1202号 代表取締役　上田英彦	平成15年　6月27日就任 平成15年　7月11日登記 平成16年　6月24日退任 平成16年　7月　7日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１６年１０月　１日就任 平成１６年１０月　１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	大阪府池田市畑四丁目１３番３号 代表取締役　青木初夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	大阪府高槻市真上町六丁目６５番２号 代表取締役　野木森雅郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　日巻洋之	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	監査役　佐々木典夫	平成１２年　６月２９日就任 平成１２年　７月１２日登記
	監査役　佐々木典夫	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　立川四郎	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	監査役　大谷豊達	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	監査役　大谷豊達	平成１６年　６月２４日重任 平成１６年　７月　７日登記
		平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　山田英夫	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	監査役　山田英夫	平成１６年　６月２４日重任 平成１６年　７月　７日登記
	監査役　斎藤健一郎	平成１５年　６月２７日就任 平成１５年　７月１１日登記
	監査役　松尾眞	平成１５年　６月２７日就任 平成１５年　７月１１日登記
		平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	監査役　石井政弥	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　小林幹司	平成１７年　４月　１日就任 平成１７年　４月　１日登記
支　店	１ 東京都中央区日本橋本町二丁目４番７号	
	東京都中央区日本橋本町二丁目５番７号	平成１４年　９月２８日移転 平成１４年１０月　４日登記
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月２４日移転 平成１７年　２月　１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　１２／２１

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	2 大阪市中央区北浜三丁目７番１２号	
	大阪市中央区瓦町三丁目６番５号	平成１５年　５月１９日移転 平成１５年　５月２１日登記
	3 北海道札幌市中央区大通西五丁目９番地１	
	4 名古屋市中区栄一丁目１０番２１号	
	名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	5 宮城県仙台市青葉区大町二丁目２番２５号	
	6 福岡市博多区博多駅東一丁目１８番２５号	
	福岡市博多区下川端２番１号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	7 東京都中央区日本橋本町二丁目５番６号	
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
	東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	8 香川県高松市寿町一丁目４番８号	
	香川県高松市サンポート２番１号	平成１６年　３月２２日移転 平成１６年　３月２２日登記
	9 広島県広島市中区大手町三丁目７番２号	
	広島市中区大手町二丁目１１番１０号	平成１７年　４月　１日移転 平成１７年　４月　１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	１０ 台北市南京東路三段２８７号	平成１６年１０月３１日廃止 平成１６年１１月　１日登記
	１１ 横浜市中区太田町六丁目８４番地２ 横浜市西区みなとみらい二丁目２番１号	平成１５年　２月２５日移転 平成１５年　３月　４日登記
	１２ 京都市中京区烏丸通二条下る秋野々町５１３番地	
	１３ 東京都中央区日本橋本町二丁目５番６号 東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
	さいたま市大宮区桜木町一丁目７番地５	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	１５ 仙台市青葉区大町二丁目２番２５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１６ 東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１７ 千葉市美浜区中瀬二丁目６番地	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１８ 東京都中央区日本橋本町一丁目５番９号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１９ 名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日設置 平成１７年　４月　１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	２０ 石川県金沢市本町一丁目５番２号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２１ 大阪市中央区瓦町三丁目６番５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２２ 神戸市中央区磯辺通三丁目１番７号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２３ 岡山市下石井一丁目１番３号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２４ 福岡市博多区下川端２番１号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
新株予約権	第１回新株予約権 新株予約権の数 １４１０個 新株予約権の目的たる株式の種類及び数 当社普通株式　１４万１０００株 新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。 なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。 調整後付与株式数　＝　調整前付与株式数　×　分割または併合の比率 また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。 各新株予約権の発行価額 無償	

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

各新株予約権の行使に際して払込みをすべき金額
　各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
　行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
　なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使及び「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換の場合を除く。）次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

　上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
　また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
　さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
　平成１７年７月１日から平成２５年６月２７日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
　各新株予約権の一部行使はできないこととする。
会社が新株予約権を消却することができる事由及び消却の条件
　①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。
　②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。

平成１５年　７月１１日登記

第２回新株予約権
　新株予約権の数
　　１４７０個

新株予約権の目的たる株式の種類及び数
当社普通株式１４万７０００株
新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。
なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。
調整後付与株式数＝調整前付与株式数×分割または併合の比率
また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。
各新株予約権の発行価額
無償
各新株予約権の行使に際して払込みをすべき金額
各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使、「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換及び商法第２２１条ノ２の規定（単元未満株式の売渡請求）に基づく自己株式の譲渡の場合を除く。）は、次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
平成１８年７月１日から平成２６年６月２４日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
各新株予約権の一部行使はできないこととする。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	会社が新株予約権を消却することができる事由及び消却の条件 ①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。 ②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。 平成１６年　７月　７日登記
転換社債	第３回無担保転換社債 転換社債の総額 金１４９億２１００万円 金１４９億１５００万円 平成１３年　４月３０日変更　平成１３年　５月　９日登記 金１４９億１３００万円 平成１４年　４月３０日変更　平成１４年　５月１０日登記 金１４９億１１００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記 金１４９億３００万円 平成１４年１２月３０日変更　平成１５年　１月１４日登記 転換の条件 転換により発行する株式１株の発行価額（以下転換価額という。）は、下記(1)によって決定し、転換により発行すべき株式数は、次のとおりとする。ただし、本社債額面金額の一部及び利息については、転換を請求することはできない。 株式数＝各社債権者が転換請求のため提出した本社債額面金額の総額 ÷ 転換価額 この場合に、１株未満の端数を生じたときは、その端数に相当する社債額面金額は、額面１００円につき１００円の割合で償還する。 (1)　転換価額　金４４１３円 (2)　転換価額の調整 転換価額は、当社が本社債発行後、時価を下回る払込金額で新株式を発行する場合には、次の算式により調整される。 調整後転換価額 ＝ 調整前転換価額 × (既発行株式数＋新発行株式数×１株当りの払込金額÷時価) ÷ (既発行株式数＋新発行株式数) なお、株式配当、無償交付、株式の分割もしくは併合等が行われる場合にも調整されるものとする。ただし、転換により当社記名式額面普通株式を発行する場合で、調整後の転換価額が当社記名式額面普通株式の額面金額を下回るときは、当該額面金額を転換価額とする。 転換によって発行すべき株式の内容 当社記名式額面普通株式（１株の額面金額５０円） ただし、本社債の転換により発行する株式を当社記名式無額面普通株式とした場合は、当社記名式無額面普通株式。

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	転換の請求をすることのできる期間 昭和６２年９月１日から昭和７７年１２月３０日まで 各転換社債の金額 金１００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる
	平成１４年１２月３０日転換請求期間満了　平成１５年　１月１４日登記
	２０１４年満期円貨建転換社債 転換社債の総額 金１８８億８０００万円 金１８６億８０００万円　平成１１年　５月３１日変更　平成１１年　６月１４日登記 金１７６億９０００万円　平成１１年　６月３０日変更　平成１１年　７月１２日登記 金１１２億３０００万円　平成１１年　７月３１日変更　平成１１年　８月１０日登記 金１０５億４０００万円　平成１１年　８月３１日変更　平成１１年　９月１３日登記 金９６億５０００万円　平成１１年１０月３１日変更　平成１１年１１月１２日登記 金９４億４０００万円　平成１１年１１月３０日変更　平成１１年１２月１３日登記 金９２億２０００万円　平成１１年１２月３１日変更　平成１２年　１月１４日登記 金９１億８０００万円　平成１２年　１月３１日変更　平成１２年　２月１４日登記 金８３億９０００万円　平成１２年　２月２９日変更　平成１２年　３月１４日登記 金８１億５０００万円　平成１２年　４月３０日変更　平成１２年　５月１２日登記 金８１億４０００万円　平成１２年　５月３１日変更　平成１２年　６月１３日登記 金７５億１０００万円　平成１２年　７月３１日変更　平成１２年　８月　８日登記 金７２億９０００万円　平成１２年　８月３１日変更　平成１２年　９月１１日登記 金６６億４０００万円　平成１２年１１月３０日変更　平成１２年１２月　８日登記 金６６億１０００万円　平成１２年１２月３１日変更　平成１３年　１月１２日登記 金６６億円　平成１３年　１月３１日変更　平成１３年　２月　８日登記 金６５億円　平成１４年　２月２８日変更　平成１４年　３月１１日登記 金６４億８０００万円　平成１４年　５月３１日変更　平成１４年　６月１２日登記

	金６４億７０００万円　平成１６年　４月３０日変更　平成１６年　５月１３日登記 金５８億２０００万円　平成１６年１０月３１日変更　平成１６年１１月１０日登記 金５０億２０００万円　平成１７年　１月３１日変更　平成１７年　２月　８日登記 転換の条件 本社債は、その額面金額に対し、下記の転換価額につき当社額面普通株式１株の割合をもって当社額面普通株式に転換することができる。 但し、転換の際に生じる１株未満の端数は、これを切り捨て、現金による調整は原則として行わない。 イ．当初の転換価額は、１株当り金１９７９円とする。 ロ．転換価額の修正 １９９８年３月３１日、２００４年３月３１日及び２００９年３月３１日（以下それぞれ「決定日」という。）より東京証券取引所における当社額面普通株式の普通取引の終値のある４５連続営業日前に開始する３０連続営業日における終値の平均値に１．０２５を乗じ１円未満を切り上げた額が、当該各決定日に有効な転換価額を１円以上下回る場合には、転換価額は１９９８年４月２２日、２００４年４月２２日及び２００９年４月２２日（以下それぞれ「効力発生日」という。）以降、上記により算出された各金額（但し、決定日から効力発生日の前日までに効力の発生した下記ハ．の調整を受ける。）に修正されるものとする。但し、転換価額は、かかる修正の結果として当初の転換価額（但し、下記ハ．の調整がなされた場合には、調整後の金額）の５０％未満に修正されることはなく、５０％未満となる場合は、かかる転換価額の５０％にあたる金額の１円未満を切り上げた価額とする。 ハ．転換価額の調整 転換価額は、当社が本社債発行後、当社の普通株式の時価を下回る払込金額で新たに普通株式を発行する場合、次の算式により調整される。 $$\text{調整後転換価額} = \text{調整前転換価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新発行株式数} \times \text{１株当り払込金額}}{\text{１株当り時価}}}{\text{既発行株式数} + \text{新発行株式数}}$$ 又、転換価額は、株式の分割・併合、当社の普通株式の時価を下回る当初転換価額又は新株引受権行使価額での転換社債又は新株引受権付社債の発行その他一定の場合にも適宜調整される。但し、転換価額は当社額面普通株式の額面金額を下回らないものとする。 転換によって発行すべき株式の内容 当社額面普通株式（現在の１株の額面金額５０円） 転換の請求をすることのできる期間 １９９４年５月９日から２０１４年３月２４日の営業終了時（転換請求地時間）までとする。 各転換社債の金額 金１０００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

会社分割	平成１６年１０月１日東京都中央区日本橋本町二丁目７番１号ゼファーマ株式会社に分割 平成１６年１０月　１日登記
吸収合併	大阪市中央区道修町三丁目４番７号藤沢薬品工業株式会社を合併 平成１７年　４月　１日登記
登記記録に関する事項	平成元年法務省令第１５号附則第３項の規定により 平成１１年　５月２０日移記

これは登記簿に記録されている閉鎖されていない事項の全部であることを証明した書面である。

平成１７年　４月　７日

東京法務局
登記官　　大　庭　元　行

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　２１／２１

OBLON
SPIVAK
McCLELLAND
MAIER
&
NEUSTADT
P.C.

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

DOCKET NO.: 312582US0SD

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

ATTENTION: MAIL STOP PATENT TERM EXTENSION

RE: Application Serial No.: 08/295,782
Patentees: Hitoshi NISHIYAMA et al
PCT Filed: March 8, 1993
Patent No.: 5,514,773
Issued: May 7, 1996
For: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF
Group Art Unit: 1811
Examiner: RUSSEL, J. E.

SIR:

Attached hereto for filing are the following papers:

AMENDED APPLICATION FOR PATENT TERM EXTENSION
WITH EXHIBITS A-H (3 COPIES)

Our credit card payment form in the amount of $0.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R §1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. §1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Registration No. 32,884

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF	:
HITOSHI NISHIYAMA ET AL	: GROUP ART UNIT: 1811
SERIAL NO: 08/295,782	: EXAMINER: RUSSEL, J. E.
PCT FILED: MARCH 8, 1993	: PATENT NO. 5,514,773
FOR: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF	: ISSUED: MAY 7, 1996

AMENDED APPLICATION FOR EXTENSION OF PATENT TERM UNDER

35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, AND 1.778

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Applicant, Astellas Pharma Inc., of Tokyo, Japan, hereby submits this application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, and 1.778 for U.S. Patent No. 5,514,773 ("the '773 patent").

Applicant, Astellas Pharma Inc., is the assignee of the '773 patent, as evidenced by assignments recorded on October 11, 1994, at Reel/Frame 007276/0013 and on December 12, 2005, at Reel/Frame 017073/0257. Copies of the Patent Assignment Abstract of Title page for the '773 patent and the first assignment are attached hereto as Exhibit A.

The applicant for and the holder of marketing approval for PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution, the approved product which is relevant to

this application, is Bayer HealthCare LLC, Animal Health Division. Bayer HealthCare LLC, Animal Health Division is the exclusive licensee of Astellas Pharma Inc. for the '773 patent. Astellas Pharma Inc. has been authorized by Bayer HealthCare LLC, Animal Health Division to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution. A copy of a letter from Bayer HealthCare LLC, Animal Health Division which authorizes Astellas Pharma Inc. to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution is attached hereto as Exhibit B.

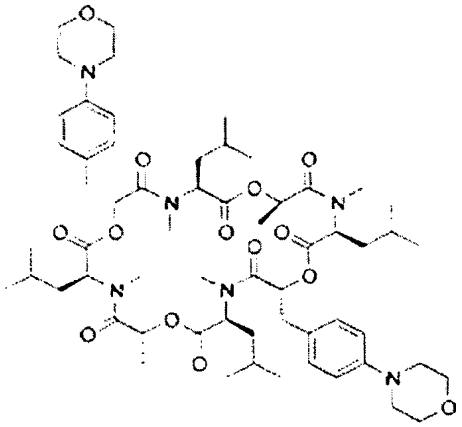
Two additional copies of this application (for a total of three copies) are being submitted herewith (37 C.F.R. § 1.740(b)).

I. Complete Identification of the Product (37 C.F.R. § 1.740(a)(1)).

The approved product is PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution (hereinafter PROFENDER®), which is the registered name for topical solution of lyophilized emodepside and praziquantel. PROFENDER® is a combination product of emodepside and praziquantel for use in the treatment and control of hookworm, roundworm, and tapeworm infections.

Emodepside, a semi-synthetic molecule, is a cyclic depsipeptide. The chemical name for emodepside is cyclo[D-2-hydroxypropanoyl-N-methyl-L-leucyl-2-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl]. Emodepside acts at the neuromuscular junction by stimulating presynaptic receptors

belonging to the secretin receptor family, resulting in paralysis and death of the parasite. The structural formula of emodepside is:



Praziquantel is an isoquinoline cestocide. The chemical name for praziquantel is 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazine-2,1-a-isoquinoline-4-one.

A copy of the package insert for PROFENDER® is attached hereto at Exhibit C.

II. Complete Identification of the Federal Statute Underwhich Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell PROFENDER® was granted under 21 U.S.C. § 360(b) (section 512 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of the Date on which the Product Received Approval (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for PROFENDER® was granted under 21 U.S.C. § 360(b) (section 512 of the Federal Food, Drug, and Cosmetic Act) on June 29, 2007, and copy of the approval letter is attached hereto as Exhibit D.

IV. Identification of Each Active Ingredient and Statement that Each Active Ingredient has not been Previously Approved or when Each Active Ingredient was Approved (37 C.F.R. § 1.740(a)(4)).

The approved combination product includes the active ingredients emodepside and praziquantel, and has never been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(A) Emodepside:

Emodepside has not been previously approved for any commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360(e)).

(B) Praziquantel:

Praziquantel has been previously approved for commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360(e)) as indicated by the following information:

1. Alone

NADA number: 111-607

Approval Date: July 16, 1993

For use in dogs and cats for the removal of canine and/or feline cestodes; Dogs: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. Cats: *Taenia taeniaeformis* and *Dipylidium caninum*.

2. Alone

NADA number: 111-798

Approval Date: July, 16, 1993

For use in dogs for the removal of the following canine cestodes: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. For use in cats for the removal of the following feline cestodes: *Dipylidium caninum* and *Taenia taeniaeformis*.

3. Alone

ANADA number: 200-176

Approval Date: October 16, 2002

For use in dogs and cats for the removal of the following canine and/or feline cestodes. Dogs: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and *Echinococcus multilocularis*. Cats: *Taenia taeniaeformis* and *Dipylidium caninum*.

4. Alone

ANADA number: 200-265

Approval Date: August 28, 2003

For use in dogs for the removal of the following canine cestodes: *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus* and for the removal and control of *Echinococcus multilocularis*. For use in cats for the removal of the following feline cestodes: *Dipylidium caninum* and *Taenia taeniaeformis*.

5. With Febantel

NADA number: 133-953

Approval Date: September 12, 1991

For use in dogs and cats for the removal of the following canine and/or feline

nematode parasites: Dogs: Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxocara leonina*), Whipworms (*Trichuris vulpis*), Tapeworms (*Dipylidium caninum* and *Taenia pisiformis*). Cats: Hookworms (*Ancylostoma tubaeforme*), Ascarids (*Toxocara cati*), Tapeworms (*Dipylidium caninum* and *Taenia taeniaeformis*).

6. With Febantel and Pyrantel Pamoate

NADA number: 141-007

Approval Date: February 10, 2003

For use in dogs for the removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*), Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichuris vulpis*).

7. With Ivermectin

NADA number: 141-214

Approval Date: October 28, 2005

For treatment and control of the following parasites in horses: Tapeworms - *Anoplocephala perfoliata*, Large strongyles (adults) - *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus*, *Triodontophorus spp.* including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; Small Strongyles (adults, including those resistant to some benzimidazole class compounds) – *Coronocyclus spp.* including *C. coronatus*, *C. labiatus*, and *C. labratus*, *Cyathostomum spp.* Including *C. catinatum* and *C. pateratum*, *Cylicocyclus spp.* including *C. insigne*, *C. leptostomum*, *C. nassatus*, and *C. brevicapsulatus*, *Cylicodontophorus spp.*, *Cylicostephanus spp.* including *C. calicatus*, *C. goldi*, *C. longibursatus*, and *C. minutus*, and *Petrovinema poculatum*; Small

Strongyles - fourth-stage larvae; Pinworms (adults and fourthstage larvae)-*Oxyuris equi*; Ascarids (adults and third- and fourth-stage larvae)-*Parascaris equorum*; Hairworms (adults)-*Trichostrongylus axei*; Large-mouth Stomach Worms (adults)- *Habronema muscae*; Bots (oral and gastric stages)- *Gasterophilus spp.* including *G. intestinalis* and *G. nasalis*; Lungworms (adults and fourth-stage larvae)-*Dictyocaulus arnfieldi*; Intestinal Threadworms (adults)-*Strongyloides westeri*; Summer Sores caused by *Habronema* and *Draschia spp.* cutaneous third-stage larvae; Dermatitis caused by neck threadworm microfilariae of *Onchocerca sp.*

8. With Ivermectin

NADA number: 141-215

Approval Date: September 16, 2005

For treatment and control of the following parasites in horses:Tapeworms *Anoplocephala perfoliata,* Large Strongyles (adults) *Strongylus vulgaris* (also early forms in blood vessels), *Strongylus edentatus* (also tissue stages), *Strongylus equines, Triodontophorus* spp., Small Strongyles (adults, including those resistant to some benzimidazole class compounds), *Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp., Small Strongyles (fourth-stage larvae), Pinworms (adults and fourth-stage larvae), *Oxyuris equi,* Ascarids (adults and third- and fourth-stage larvae), *Parascaris equorum,* Hairworms (adults), *Trichostrongylus axei,* Large-mouth Stomach Worms (adults), *Habronema muscae,* Bots (oral and gastric stages), *Gasterophilus* spp., Lungworms (adults and fourth-stage larvae), *Dictyocaulus arnfieldi,* Intestinal Threadworms (adults), *Strongyloides westeri,* Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae, Dermatitis caused by Neck threadworm microfilariae, *Onchocerca* sp.

9. With Ivermectin and Pyrantel Pamoate

NADA number: 141-257

Approval Date: October 13, 2006

For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) and for the treatment and control of roundworms (*Toxocara canis*, *Toxascaris leonina*), hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*) and tapeworms (*Dipylidium caninum*, *Taenia pisiformis*).

10. With Pyrantel Pamoate

NADA number: 141-008

Approval Date: September 29, 1993

For use in cats to remove Tapeworms (*Dipylidium caninum, Taenia taeniaeformis*), Hookworms (*Ancylostoma tubaeforme*) and Large Roundworms (*Toxocara cati*).

11. With Moxidectin

NADA number: 141-216

Approval Date: May 14, 2003

For the treatment and control of gastrointestinal parasites of horses and ponies.

V. Statement that Application is being Submitted within the Sixty Day Period (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f), and the last day on which the application could be submitted is August 28, 2007.

VI. Complete Identification of the Patent (37 C.F.R. § 1.740(a)(6)).

The patent for which an extension is being sought is U.S. Patent No. 5,514,773 ("the '773 patent"), which issued May 7, 1996. The inventors listed on the face of the '773 patent are Hitoshi Nishiyama, Masaru Ohgaki, Ryo Yamanishi, and Toshihiko Hara. The '773 patent was filed as a PCT application on March 8, 1993, entered the U.S. national phase on September 12, 1994 (§ 317 date), issued on May 7, 1996, and has an un-extended expiration date of May 7, 2013.

VII. A Copy of the Patent for which Extension of Term is being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '773 patent is attached hereto as Exhibit E.

VIII. Copies of any Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments, or Reexamination Certificates Issued in the Patent (37 C.F.R. § 1.740(a)(8)).

Applicants state on the record that no disclaimers or certificates of correction have been filed or issued in the '773 patent and that no reexamination certificate has been issued in the '773 patent.

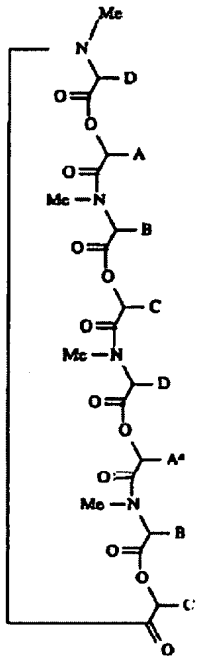
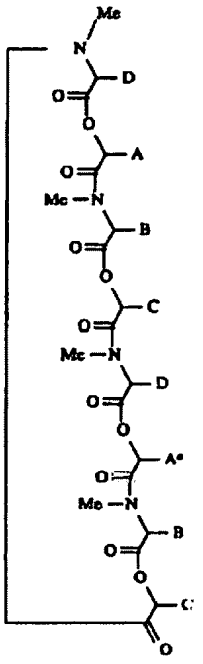
Copies of the receipts of maintenance fee payment for the first and second maintenance fees in the '773 patent are attached hereto as Exhibit F.

IX. Statement that the Patent Claims the Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, PROFENDER®, is claimed in the '773 patent. Specifically, the '773 patent claims the compound emodepside, itself, and compositions which comprise emodepside. Since PROFENDER® contains emodepside, the claims of the '773 patent cover PROFENDER™.

(A) Claims which Read on the Approved Product (37 C.F.R. § 1.740(a)(9)(i)).

The following chart sets forth the relationship between the approved product and the claims of the '773 patent which read on the approved product.

Claim of the '773 Patent	PROFENDER®
1. A compound of the general formula (I):	PROFENDER® contains emodepside, which has the structure of formula (I):
	

wherein A is a substituted benzyl group or a phenyl group which may have substituent(s), A^a is a benzyl group which may have substituent(s) or a phenyl group which may have substituent(s), B and D are each lower alkyl, and C is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof.	in which A and A^a are each benzyl groups which are substituted with morpholino groups; B and D are both isobutyl groups; and C is a methyl group.
3. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by morpholino, dimethylamino or methoxy.	PROFENDER® contains emodepside, which has the structure of formula (I) in which A and A^a are each benzyl groups which are substituted with morpholino groups.
5. A compound of the formula: [structure omitted].	PROFENDER® contains emodepside, which has the structure of the formula shown in claim 5.
9. An anthelmintic agent which comprises a compound or a pharmaceutically acceptable salt thereof of claim 1 as an active ingredient.	As explained above, PROFENDER® is approved for the treatment of hookworm, roundworm, and tapeworm infections and contains a compound according to Claim 1 of the '773 patent, emodepside.

10. The compound of claim 1 wherein B and D are each an isobutyl group.	PROFENDER® contains emodepside, which has the structure of formula (I) in which B and D are both isobutyl groups.

B. Claims which Read on the Method of Manufacturing the Approved Product (37 C.F.R. § 1.740(a)(9)(iii)).

The following chart sets forth the relationship between the approved product and the claims of the '773 patent which read on the method of manufacturing the approved product.

Claim of the '773 Patent	PROFENDER®
7. A process for preparation of a compound of the general formula: [structure omitted] or a salt thereof, which comprises subjecting a compound of the general formula: [structure omitted] or a salt thereof, to a monoalkylation reaction followed by an intramolecular reaction, wherein B and D are each lower alkyl, C is hydrogen or lower alkyl, A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and A^5 is a benzyl group substituted by cyclic	PROFENDER® contains emodepside, which has the recited structure of the product, in which in which A^5 is a benzyl group which is substituted with a morpholino; B and D are both isobutyl groups; and C is a methyl group.

amino, or a benzyl group substituted by cyclic amino and lower alkoxy.	
12. The process of claim 7 wherein B and D are each an isobutyl group.	PROFENDER® contains emodepside, which has the recited structure of the product, in which in which B and D each an isobutyl groups.

Thus, Claims 1, 3, 5, 9, and 10 cover the approved product itself, while Claims 7 and 12 cover methods of manufacturing the approved product.

X. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) for a Patent Claiming a New Animal Drug (37 C.F.R. § 1.740(a)(10)(ii)).

(A) The Effective Date of the INAD and the INAD number (37 C.F.R. § 1.740(a)(10)(ii)(A)).

The effective date for the INAD (date an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective) for the approved product is June 2, 2000, and the INAD number for the approved product is 10-753.

(B) The Date on which the NADA was Initially Submitted and the NADA Number (37 C.F.R. § 1.740(a)(10)(ii)(B)).

The NADA for the approved product was initially submitted on May 15, 2007, and the NADA number for the approved product is 141-275.

(C) The Date on which the NADA was Approved (37 C.F.R. § 1.740(a)(10)(ii)(C)).

NADA 141-275 was approved on June 29, 2007.

XI. Brief Description of Significant Activities Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period and the Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A list of significant activities undertaken by the marketing applicant during the INAD and the NADA and the significant dates applicable thereto is provided in Table 1 below.

Table 1.

Date To FDA	Date From FDA	Activity
5/30/2000		Request Establishment of an INAD for the Development of an anthelmintic topical solution for cats and kittens. Request for a Development Plan Meeting and submission of the Development Plan.
	6/2/2000	Assign INAD# 10-753
	9/25/2000	A0000; FDA meeting minutes for 7/20/00 Development plan meeting. Granted environmental waiver for INAD.
11/2/2000		Letter responding to FDA's Dev. Plan meeting minutes re: GMP status of starting material.
	12/22/2000	G0001; Letter reconfirming GMP requirement for starting material.
3/16/2001		Submit Model protocol for review - Heartworm disease #151-087
3/16/2001		Submit model protocol for review - immature nematodes #151-076
3/16/2001		Submit model protocol for review - mature nematodes & cestodes #151-078
4/3/2001		Submit "Notice of Intent to Import Clinical Material" to FDA
	6/7/2001	E0004; Protocol Acceptable Letter w/minor comments -mature nematodes/cestodes
	6/21/2001	E0002; Protocol Unacceptable (agreement reached in 7/12 phone call) - Heartworms
	6/21/2001	E0003; Protocol Unacceptable (agreement reached in 7/12 phone call) - Immatures
9/17/2001		Submit 4 safety protocols for review (Dose Tol., Gen.Safety, Oral & HW+ cats)
	11/8/2001	E0006; Safety Protocols (4) submitted 9/17/01 Unacceptable
2/18/2002		Faxed safety questions to CVM concerning 11/8/01 letter
4/9/2002		Resubmitted 4 Safety protocols (Dose Tol., Gen.Safety, Oral & HW+ cats)
4/24/2002		Submitted copy of final signed efficacy protocol #151.086 (T. Taeniaformis)
4/25/2002		Submitted copy of final signed efficacy protocol #141.000 (mature T. cati)
4/25/2002		Submitted copy of final signed efficacy protocol #151.088

		(heartworm)
5/1/2002		Submission of field trial protocol for review (#151.095)
5/1/2002		Submitted copy of final signed efficacy protocol #141.011 (immature A. tubaeforme)
5/1/2002		Submitted copy of final signed efficacy protocol #141.014 (immature T. cati)
5/1/2002		Submitted copy of final signed efficacy protocol #141.710 (E. multilocularis)
5/1/2002		Submitted copy of final signed efficacy protocol #151.076 (immature A. tubaeforme)
5/13/2002		Submitted copy of final signed efficacy protocol #151.077 (mature T. cati)
5/13/2002		Submitted copy of final signed efficacy protocol #151.083 (D. caninum)
6/14/2002		Submitted copy of final signed efficacy protocol #151.084 (D. caninum)
6/14/2002		Submitted copy of final signed efficacy protocol #151.075 (mature A. tubaeforme)
6/14/2002		Submitted copy of final signed efficacy protocol #151.078 (immature T. cati)
6/14/2002		Submitted copy of final signed efficacy protocol #151.085 (T. taeniaeformis)
6/17/2002		Notice of Intent to Import a New Animal Drug for Clinical Trials #2
7/1/2002		Telephone call from Dr. Oeller (CVM reviewer) w/changes to Gen Safety Protocol
7/3/2002		Submitted revised General Kitten Safety Protocol (see 15 & 16 above)
7/8/2002		Submitted copy of final signed efficacy protocol #151.080 (mature T. leonina)
7/8/2002		Submitted copy of final signed efficacy protocol #151.081 (immature T. leonina)
7/8/2002		Submitted copy of final signed efficacy protocol #151.082 (immature T. leonina)
7/12/2002		Submitted copy of final signed efficacy protocol #151.503 (mature A. tubaeforme)
	7/24/2002	E0008, E0025; FDA acceptable letter w/statistical comments on 4 safety protocols (see 33 above)
7/30/2002		Telephone call w/Dr. Luddy (CVM) re: natural infection mature T. leonina study
8/2/2002		Telephone call w/Dr. Luddy (CVM) re: need to do Heartworm+ safety study
	8/5/2002	FDA letter re: review of field trial protocol (see #20 above) - not acceptable
8/6/2002		Submitted copy of final signed efficacy protocol #141.084 (immature T. cati)
8/22/2002		Submitted electronic teleconference request for 9/17 w/ Drs Oeller & Luddy

9/10/2002		Submitted copy of final signed efficacy protocol #141.711 (E. multilocularis)
9/17/2002		Phone Conference Field trial Prot.- Minor corrections, resubmission not needed
	9/26/2002	Z0031;CVM minutes to 9/17/02 phone conference
	11/11/2002	Phone message from Dr. Luddy re: CVM recommendation to do heartworm safety study to allow proper labeling
1/15/2003		E-mail to Dr. Oeller (CVM) re: proposal to change from 3 to 1 dosing on field trial (protocol #151.095)
	1/17/2003	E-mail from Dr. Oeller (CVM) agreeing to change to 1 dosing on field trial 151.095
1/23/2003		Submitted copy of final signed efficacy protocol #151.599 (mature T. leonina)
1/23/2003		Submitted copy of final signed efficacy protocol #151.601 (D. caninum)
1/31/2003		Phone Conversation w/B. Luddy (CVM) re: cat death in study 151.083
2/7/2003		Phone conversation and follow-up e-mail to D. Oeller (CVM) re: 3rd T.cati study
	2/12/2003	E-mail from D. Oeller (CVM) accepting proposal on T. cati - 2 group confirmation study
2/12/2003		Submitted information on cat from study 151.083 per conversation w/B. Luddy 1/31/03
3/10/2003		Submitted copy of final signed efficacy protocol #151.614 (immature T. leonina)
3/10/2003		Submitted copy of final signed efficacy protocol #151.619 (T. cati - natural infections)
3/25/2003		Notice of Intent to Import a New Animal Drug for Clinical Trials #3
4/8/2003		Submitted copy of final signed efficacy protocol #151.629 (mature T. leonina)
6/13/2003		Submitted copy of final signed efficacy protocol #151.640 (mature T. leonina)
8/4/2003		Submitted copy of final signed efficacy protocol #151.652 (T. taeniaeformis)
10/15/2003		Submitted copies of signed protocols 151.095TX1 & MO1 + List of new investigators
10/22/2003		Submitted copy of signed field trial protocol (151.095-SC)
11/10/2003		Submitted copy of signed field trial protocol (151.095-VA)
12/29/2003		CMC Phased Technical Section submitted to CVM
1/7/2004		Update meeting with CVM on Safety & Efficacy
1/26/2004		Submitted copy of signed field trial protocol (151.095-ON)
1/29/2004		Submitted Copy of signed field trial protocol (151.095-BC)
3/24/2004		Submitted copy of final signed efficacy protocol #151.732 (immature/adult) T. leonina
3/24/2004		Submitted copy of final signed efficacy protocol #151.733 (immature/adult) T. leonina
3/25/2004		Submitted Environmental Assessment waiver request

	5/6/2004	CVM letter approving Environmental Technical Section submitted 3/25/04
	6/30/2004	CVM incomplete letter on 29 Dec03 CMC Tech Section submission
3/29/2004		Submission of Information concerning ADE in field trial (151.095-SC)
6/28/2004		Submission of Phased Target Animal Safety Section (27 Volumes)
9/27/2004		Submission of Phased Effectiveness Technical Section (86 Volumes)
11/9/2004		Amendment 1 to Phased Safety Section (s:6/28/04) - data spreadsheets for 4 pivotal studies
	12/04 - 4/05	Various calls from CVM reviewer Cacia Masser with questions concerning Efficacy data
2/15/2005		Response submitted to CVM 6/30/04 CMC incomplete letter
2/17/2005		Amendment #1 to 27SEP04 Phased Efficacy Section - to formally submit information previously provided to reviewer by email
3/3/2005		Amendment #2 to 27SEP04 Phased Efficacy Tech. Section - copies of emails between Bayer and CVM concerning efficacy discussions during review
	4/28/2005	CVM incomplete letter on 28JUN04 Safety Tech Section submission
	8/5/2005	CVM Technical Section Complete Letter for 27SEP04 Efficacy submission
	8/9/2005	2nd CVM CMC incomplete letter on 2/15/04 CMC response
	7/14-28/2005	3 phone calls from CVM with questions on efficacy data and FOI
2/22/2006		Sent Histopathology slides to CVM for review as part of Safety response
2/23/2006		Response submitted to 28APR05 Safety Tech. Section incomplete letter
3/30/2006		Response to 2nd CVM CMC incomplete letter dated 9AUG05
	6/06-10/9/06	Various calls from CVM reviewer Ann Stohlman with questions concerning safety submission/FOI
7/20/2006		Amendment #1 to 23FEB06 Safety Tech. Section response - complete copies of several references
	9/28/2006	CMC Tech. Section complete Letter (I-0101753-P-0094) for 29DEC03 Tech Section as amended
10/3/2006		Conversation w/Dr. Dennis Bensley (CVM) about statements in CMC complete letter. New requirement for foreign manufacturing sites - final product validation report and protocol must be submitted prior tp distributing product.
	10/13/2006	CVM Safety Technical Section complete Letter for 28JUN04 Tech Section as amended
	10/17/2006	Histology slides (sent 2/22/06) returned to Bayer and on to Stillwell
10/19/2006		Conversation between Bruce Martin and Dr. Steve Vaughn (CVM) concerning Bayer's plan to add "pregnant woman"

		warning statement to label.
12/13/2006		"All Other Information" Minor Technical Section is submitted
12/22/2006		"Labeling" Minor Technical Section is submitted
1/5/2007		Amendment #1 to "All Other Info" Tech. Section - abstract of Japanese Field trial
2/07 - 4/07		Various calls from CVM reviewer Ann Stohlman with questions concerning Labeling/FOI & All Other Info
4/12/2007		Amendment #2 to "All Other Info" Tech. Section - Draft of 3rd PSUR
4/13/2007		Amendment #3 to "All Other Info" Tech. Section - Copy of report referenced in 3rd PSUR ("Comparative in vitro Dermal Absorption using Human and Rat Skin").
	4/23/2007	"All Other Information" Tech. Section complete Letter (I-0101753-M-0096) for 13DEC06 Tech Section as amended
4/25/2007		Amendment #1 to 22DEC06 "Labeling" Tech. Section - revised facsimile labeling
	5/2/2007	CVM telephone call requesting final label changes
5/3/2007		Amendment #2 to 22DEC06 "Labeling" Tech. Section - revised facsimile labeling
	5/9/2007	FOI Summary Tech. Section complete Letter (I-0101753-Q-0098) with final FOI Summary attached
	5/11/2007	Labeling Tech. Section complete Letter (I-0101753-M-0097) for 22DEC06 Tech Section as amended
5/15/2007		Administrative NADA submitted to CVM
	5/18/2007	Letter received from CVM DocCenter assigning NADA number 141-275
5/30/2007		Amendment #1 to Administrative NADA submitted after telephone call with CVM concerning a spelling error on all 3 cartons
6/4/2007		Amendment #2 to Administrative NADA submitted after telephone call with CVM concerning a spelling error on all 3 cartons
	6/8/2007	Call from CVM requesting a correction to the ADVERSE REACTION section of the product insert.
6/8/2007		Amendment #3 to Administrative NADA submitting revised insert per CVM request.
	6/29/2007	CVM letter approving original new animal drug application NADA 141-275 for Profender

XII. Statement that in the Opinion of the Applicant the Patent is Eligible for Extension of Patent Term and Statement as to the Length of extension and how the Length was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the applicant, the '773 patent is eligible for extension. In the opinion of the applicant, the '773 patent is entitled to be extended by 1314 days, *i.e.*, the '773 patent is entitled to an extended expiration date of December 11, 2016. The extension was calculated by the method described in 37 C.F.R. § 1.778.

The number of days by which the '773 patent should be extended was calculated as follows:

A. The minimum number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.778(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.778(d)(1)-(6).

B. The minimum number of days in the regulatory review was calculated by adding the number of days pursuant to (37 C.F.R. § 1.778(c)(1)) and the minimum number of days pursuant to (37 C.F.R. § 1.778(c)(2)).

C. The number of days pursuant to (37 C.F.R. § 1.778(c)(1)) was calculated as the number of days in the period starting from the date on which INAD 10-753 was approved, June 2, 2000, and ending on the date NADA 141-275 was submitted, May 15, 2007, and determined to be 2538 days.

D. The minimum number of days pursuant to (37 C.F.R. § 1.778(c)(2)) was calculated as the number of days in the period starting from the date NADA 141-275 was submitted, May 15, 2007, and ending on the date of approval of NADA 141-275, June 29, 2007, and determined to be at least 45 days.

E. Thus, the minimum number of days in the regulatory review period under 37 C.F.R. § 1.778(c) was calculated by adding 2538 days to 45 days and determined to be 2583 days

F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.778(d)(1) was calculated by determining the number of days pursuant to each of C.F.R. §§ 1.778(d)(1)(i)-(iii).

G. Since the regulatory review period began on June 2, 2000, and since the '773 patent issued on May 7, 1996, 0 days in the regulatory review period were on or before the date on which the '773 patent issued. Thus, the number of days pursuant to C.F.R. § 1.778(d)(1)(i) was determined to be 0.

H. As set forth above, applicants have acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to C.F.R. § 1.778(d)(1)(ii) was determined to be 0.

I. The number of days pursuant to C.F.R. § 1.778(d)(1)(iii) was calculated by first subtracting the number of days pursuant to C.F.R. § 1.778(d)(1)(i), 0 days, from the number of days pursuant to 37 C.F.R. § 1.778(c)(1), 2538 days, to obtain 2538 days and then dividing that number of day in half and determined to be 1269 days.

J. The number of days pursuant to C.F.R. § 1.778(d)(1) was calculated by subtracting the number of days calculated pursuant to C.F.R. § 1.778(d)(1)(i), 0 days, and the number of days calculated pursuant to C.F.R. § 1.778(d)(1)(iii), 1269 days, from the number of days calculated pursuant to C.F.R. § 1.778(c), 2583 days, and determined to be 1314 days.

K. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(2) was calculated by adding the number of days calculated pursuant to C.F.R. § 1.778(d)(1), 1314 days, to the original term of the '773 patent (current expiration date May 7, 2013) and determined to be December 11, 2016.

L. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(3) was calculated by adding 14 years to the date of approval, June 29, 2007, and determined to be June 29, 2021.

M. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(4) was calculated by comparing the dates calculated pursuant to C.F.R. § 1.778(d)(3) and C.F.R. § 1.778(d)(4) and selecting the earlier date and determined to be December 11, 2016

N. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(5)(i) was calculated by adding five years to the original expiration date of the '773 patent (May 7, 2013) and determined to be May 7, 2018.

O. The term of the '773 patent as extended as determined by C.F.R. § 1.778(d)(5)(ii) was calculated by selecting the earlier date pursuant to C.F.R. § 1.778(d)(4) and C.F.R. § 1.778(d)(5)(i) and determined to be December 11, 2016.

P. Since the '773 patent issued after November 16, 1988, no adjustment was made under C.F.R. § 1.778(d)(6).

XIII. Statement that Applicant Acknowledges a Duty to Disclose any Information which is Material to the Determination of the Entitlement to the Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such, must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension

proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

XIV. Prescribed Fee (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j)(1) for the amount of $1,120.00 was paid in the from of a credit card form on August 24, 2007.

XV. Correspondence Information (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Power of Attorney (37 C.F.R. §§ 1.730(a)(2) and (d)).

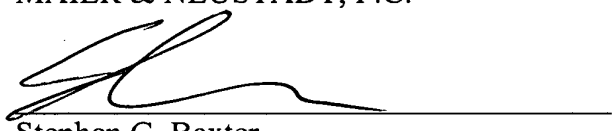
A copy of the original Power of Attorney is being submitted herewith as Exhibit G.

As can be seen from the face of the '773 patent itself, the '773 patent was originally assigned to Fujisawa Pharmaceutical Co., Ltd., of Osaka, Japan ("Fujisawa"). Effective April 1, 2005, Fujiswa became part of Astellas Pharma Inc., of Tokyo, Japan. A formal notice of the change of name has already been filed in the USPTO, and copies of the papers filed are attached hereto as Exhibit H. Oblon, Spivak, McClelland, Maier & Neustadt, P.C., remains the attorney of record for the '773 patent.

In view of the foregoing, Applicants submit that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 5514773 **Issue Dt:** 05/07/1996 **Application #:** 08295782 **Filing Dt:** 09/12/1994

Inventors: HITOSHI NISHIYAMA, MASARU OHGAKI, RYO YAMANISHI, TOSHIHIKO HARA

Title: DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF

Assignment: 1

Reel/Frame: 007276/0013 **Recorded:** 10/11/1994 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: NISHIYAMA, HITOSHI **Exec Dt:** 08/05/1994

OHGAKI, MASARU **Exec Dt:** 08/05/1994

YAMANISHI, RYO **Exec Dt:** 08/05/1994

HARA, TOSHIHIKO **Exec Dt:** 08/05/1994

Assignee: FUJISAWA PHARMACEUTICAL CO., LTD.
4-7, DOSHOMACHI 3-CHOME, CHUO-KU
OSAKA-SHI, OSAKA 541, JAPAN

Correspondent: NORMAN F. OBLON
OBLON, SPIVAK, MCCLELLAND ET AL.
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

Assignment: 2

Reel/Frame: 017073/0257 **Recorded:** 12/12/2005 **Pages:** 39

Conveyance: MERGER (SEE DOCUMENT FOR DETAILS).

Assignor: FUJISAWA PHARMACEUTICAL CO., LTD. **Exec Dt:** 04/01/2005

Assignee: ASTELLAS PHARMA INC.
3-11, NIHONBASHI-HONCHO 2-CHOME
CHUO-KU, TOKYO, JAPAN

Correspondent: OBLON, SPIVAK, MCCLELLAND, MAIER & NEUST
1940 DUKE STREET
ALEXANDRIA, VA 22314

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1-31-92

79 Rec'd PCT/PTC 11 OCT 1994

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Hitoshi NISHIYAMA
Masaru OHGAKI
Ryo YAMANISHI
Toshihiko HARA

Additional name(s) of conveying party(ies) attached? –☐ Yes –■ No

2. Name and address of receiving party(ies):

Name: FUJISAWA PHARMACEUTICAL CO., LTD.

Address: 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi
Osaka 541, JAPAN

3. Nature of Conveyance:

19

–■ Assignment –☐ Merger
–☐ Security Agreement –☐ Change of Name
–☐ Other _____

Execution Date: August 5, 1994

Additional name(s) & address(es) attached? –☐ Yes –■ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

08/295,782

B. Patent No.(s)

Additional numbers attached? –☐ Yes ■ No

95 JAN 25 PM 4:53
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ASSIGNMENT BRANCH

5. Name and address of party to whom correspondence concerning document should be mailed:

Norman F. Oblon
OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
Attorneys at Law
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $40.00

■ Enclosed
–☐ Authorized to be charged to deposit account

8. Deposit account number: 15-0030

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Norman F. Oblon
Name of Person Signing

Robert T. Pious
Registration Number 27,295

10/6/94
Date

Total number of pages comprising cover sheet: 3 18

OMB No. 0651-0011 (exp. 4/94)

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93734414

Assignment Of Application

WHEREAS, I (WE) Hitoshi Nishiyama, Masaru Ohgaki, Ryo Yamanishi and Toshihiko Hara

INSERT NAMES AND RESIDENCE ADDRESSES OF THE INVENTORS:

of 13-1-317, Kuzuharshinmachi, Neyagawa-shi, OSAKA 572 JAPAN; 3-1-58-506, Minatojimanakamachi, Chuo-ku, Kobe-shi, HYOGO 650 JAPAN, 16-3, Hoshimi-cho, Ibaraki-shi, OSAKA 567 JAPAN and 565-19, Ooaza Miyaji, Miura-mura, Inashiki-gun, IBARAKI 300-04 JAPAN

, respectively,

INSERT TITLE OF INVENTION:

have invented certain new and useful improvements in: DEPSIPEPTIDE DERIVATIVE, PRODUCTION THEREOF AND USE THEREOF,

INSERT DATE INVENTORS SIGNED DECLARATION:

for which an application for Letters Patent was executed on August 5, 1994 (Application No. 08/295,782, filed September 12, 1994), and

INSERT NAME AND ADDRESS OF COMPANY OR OTHER ASSIGNEE:

WHEREAS, Fujisawa Pharmaceutical Co., Ltd. (hereinafter referred to as "ASSIGNEE") having a place of business at: 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, OSAKA 541 JAPAN,

is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefore in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letter Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Spivak, McClelland, Maier & Neustadt, P.C. of Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

Date: August 5, 1994	Hitoshi Nishiyama	
	(Signature of Inventor) Hitoshi Nishiyama	
Date: August 5, 1994	Masaru Ohgaki	
	(Signature of Inventor) Masaru Ohgaki	
Date: August 5, 1994	Ryo Yamanishi	
	(Signature of Inventor) Ryo Yamanishi	
Date: August 5, 1994	Toshihiko Hara	
	(Signature of Inventor) Toshihiko Hara	
Date:	(Signature of Inventor)	
Date:	(Signature of Inventor)	
Date:	(Signature of Inventor)	
Date:	(Signature of Inventor)	

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OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

Bayer HealthCare
Animal Health

Ms. Mary Till
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Jessica Monachello
Patent Counsel

Re: Application for Patent Term Extension For U.S. Patent No. 5,514,773

August 21, 2007

Dear Ms. Till:

Bayer HealthCare LLC, Animal Health Division is the applicant for and the holder of marketing approval for PROFENDER® [1.98% emodepside/7.94% praziquantel] Topical Solution (hereinafter PROFENDER®). Bayer HealthCare LLC, Animal Health Division authorizes Astellas Pharma Inc. to rely on the activities of Bayer HealthCare LLC, Animal Health Division before the Food and Drug Administration in connection with the approval of PROFENDER® for the extension of the term of U.S. Patent No. 5,514,773.

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201

Phone: 913-268-2038
Fax: 913-268-2855
jessica.monachello.b@bayer.com

Very truly yours,

Jessica Monachello

Jessica J. Monachello

cc: Cynthia Hughes-Coons
Assistant General Counsel

Topical Solution

PROPENDER.

(emodepside/praziquantel)

CAUTION: Federal law (U.S.A.) restricts this drug to use by or on the order of a licensed veterinarian.

Topical Solution for the treatment and control of hookworm, roundworm and tapeworm infections in cats and kittens that are at least 8 weeks of age and weigh at least 2.2 lbs (1 kg).

DESCRIPTION:

PROPENDER [1.50% emodepside/7.94% praziquantel] Topical Solution is a clear yellow ready-to-use solution packaged in single unit dosing applicator tubes for topical (dermal) treatment of cats 8 weeks of age and older and weighing at least 2.2 lbs (1 kg). The formulation and dosage schedule is designed to provide a minimum of 1.36 mg/lb (3 mg/kg) emodepside and 5.45 mg/lb (12 mg/kg) praziquantel based on body weight.

Emodepside, a semi-synthetic molecule, is a cyclic depsipeptide. The chemical name is Cyclo [D-3-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-3-hydroxypropanoyl-N-methyl-L-leucyl-D-3-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-3-hydroxypropanoyl-N-methyl-L-leucyl].

Praziquantel is an isoquinoline cestocide. The chemical name is 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino-2,1-a-isoquinolin-4-one.

INDICATIONS:

PROPENDER Topical Solution is indicated for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats.

DOSAGE AND ADMINISTRATION:

The recommended minimum dose is 1.36 mg/lb (3 mg/kg) emodepside + 5.45 mg/lb (12 mg/kg) praziquantel as a single topical dose. A single treatment is effective and a second treatment should not be necessary. If re-infection occurs, the product can be re-applied after 30 days.

1. Select the package that correctly corresponds with the body weight of the cat. (See Table below.)

Cat Weight*	Package Size/Quantity	Volume (ml)	mg Emodepside	mg Praziquantel
2.2-5.5 lbs	Small	0.35	7.1	35
>5.5-11 lbs	Medium	0.70	13.9	69.1
>11-17.6 lbs	Large	1.12	22.0	110

* Cats over 17.6 lbs should be treated with the appropriate combination of tubes.

2. Remove one unit dose tube from the package.
3. While holding the tube in an upright position, pull the cap off the tube.
4. Turn the cap over and place the other end of cap onto the tip of the tube.
5. Twist the cap to break the seal and then remove cap from the tube.

6. Part the hair on the back of the cat's neck at the base of the head, until the skin is visible.

7. To ensure the entire contents of the tube are administered, place the tip of the tube on the skin and squeeze the entire contents directly onto the skin. Lift tube away from the skin before releasing pressure on the tube. Do not allow the cat to lick the application site.

Do not apply to broken skin or if hair coat is wet. Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for one hour. Oral exposure can cause salivation and vomiting. Treatment at the base of the head will minimize the opportunity for ingestion while grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff hair, a damp appearance of the hair, or a slight powdery residue may be observed at the treatment site. These effects are temporary and do not affect the safety or effectiveness of the product.

HUMAN WARNINGS:

Not for human use. Keep out of reach of children.

To prevent accidental ingestion of the product, children should not come in contact with the application site for twenty-four (24) hours while the product is being absorbed. Pregnant women, or women who may become pregnant, should avoid direct contact with, or wear disposable gloves when applying, this product. Studies performed in rats and rabbits suggest that emodepside may interfere with fetal development in these species.

PROPENDER topical solution may be irritating to skin and eyes. Reactions such as facial, tongue and hand swelling have been reported in humans in rare instances. Avoid contact with the application area while it is wet and wash hands thoroughly with soap and warm water after handling. People with known hypersensitivity to butylhydroxyanisole, emodepside or praziquantel should administer the product with caution. If the product accidentally gets into eyes, flush thoroughly with water. May be harmful if

Bayer HealthCare

Propender® Topical Solution
(emodepside/praziquantel)
Multiple Insert
Front

swallowed. In case of accidental ingestion or if skin or eye irritation occurs, call a poison control center or physician for treatment advice.

The Material Safety Data Sheet (MSDS) provides additional occupational safety information. For customer service or to obtain product information, including the MSDS, call 1-800-633-3796. For medical emergencies or to report an adverse reaction, call 1-800-422-9874.

PRECAUTIONS:

Safe use of this product has not been evaluated in cats less than 8 weeks of age or weighing less than 2.3 lbs (1 kg), in cats used for breeding, during pregnancy or in lactating queens. The effectiveness of this product when used before bathing has not been evaluated.

Use with caution in sick or debilitated cats. Oral ingestion or exposure should be avoided. Use with caution in heartworm positive cats. The cats enrolled in the field study were heartworm antigen and antibody negative prior to entering the study. In a laboratory study, cats artificially infected with adult heartworms and treated with PROFENDER Topical Solution had fewer worms recovered than the placebo control group. (See Animal Safety.)

ADVERSE REACTIONS:

Field study: In a controlled, double-masked field safety study, owners administered PROFENDER Topical Solution to 606 cats. Adverse reactions reported by the cat owners included licking/excessive grooming in 18 cats (3.0%), scratching treatment site in 15 cats (2.5%), salivation in 10 cats (1.7%), alopecia in 8 cats (1.3%), agitation/nervousness in 7 cats (1.2%), vomiting in 6 cats (1.0%), diarrhea in 3 cats (0.5%), eye irritation in 3 cats (0.5%), respiratory irritation in 1 cat (0.2%) and shaking/tremors in 1 cat (0.2%). All adverse reactions were self-limiting.

Laboratory effectiveness studies: One cat died 10 days after receiving PROFENDER Topical Solution. The necropsy showed chronic active cholangiohepatitis. While the use of the drug did not appear to be the direct cause of death, treatment with the drug cannot be ruled out as a contributing factor (See PRECAUTIONS). One cat treated with a vehicle placebo (formulation minus the active ingredients) showed salivation, gagging, lethargy and a swollen tongue.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in foreign markets: application site reaction (hair loss, dermatitis, pyoderma, edema, and erythema), salivation, pruritus, lethargy, vomiting, diarrhea, dehydration, ataxia, loss of appetite, facial swelling, rear leg paresis, seizures, hyperesthesia, twitching, and death.

EFFECTIVENESS:

In a total of 13 controlled laboratory studies to establish effectiveness, 149 cats were treated with PROFENDER Topical Solution. In the field study conducted at 13 veterinary clinics/hospitals, 837 purebred or crossbred cats from single and multi-cat households were enrolled to evaluate safety and effectiveness under field conditions of use. Of these, 606 received a single treatment with PROFENDER Topical Solution. Cats ranged between 3 months and 17 years of age and weighed between 0.8 lbs (0.36 kg) to 21 lbs (9.42 kg). Data from these studies demonstrated PROFENDER Topical Solution is safe and effective for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults).

ANIMAL SAFETY:

In a field study, PROFENDER Topical Solution was used in cats receiving other frequently used products including: analgesics, anti-fungals, non-steroidal anti-inflammatories, anthelmintics, antimicrobials, flea and tick products, sedatives, anesthetics, cardiac medications, antiolytics, hormonal treatments, steroids, otic and ophthalmic preparations, and vaccines.

Dose Tolerance Study in Cats: PROFENDER Topical Solution was applied topically one time to young cats at 10X the recommended label use rate. Two cats salivated. Another cat exhibited tremors and lethargy. These signs were self-limiting.

Oral Safety Studies in Cats: PROFENDER Topical Solution was administered orally at the recommended topical dose to young adult cats. The cats exhibited salivation, vomiting, tremors, abnormal gait, abnormal respiration and weight loss. These signs were self-limiting.

General Safety Study in Kittens: PROFENDER Topical Solution was topically applied at 0X (vehicle control), 1X, 3X and 5X the maximum dose to 48 healthy 8-week-old kittens every two weeks for six doses. One 5X kitten experienced salivation and tremors and another 5X kitten experienced salivation on the day of dosing. A third 5X kitten experienced tremors the day after dosing. These cats vomited within 24 hours of dosing, one each in vehicle control, 1X and 5X groups.

Safety Study in Heartworm Positive Cats: Cats artificially infected with adult heartworms harvested from dogs were treated topically with PROFENDER Topical Solution at 0X, 1X or 5X the recommended dose once a month for three treatments. Clinical signs included salivation (one 1X and three 5X cats), labored breathing (all groups) and lethargy (one 5X cat). At the study conclusion, the 1X and 5X cats had fewer live heartworms recovered than the 0X group.

STORAGE INFORMATION:

Store at or below 77°F (25°C).
Protect from freezing.

HOW SUPPLIED:

Code Number	Applications per Package
03615028	40 - 0.35 mL tubes (10 blisters of 4 tubes)
03615034	40 - 0.70 mL tubes (10 blisters of 4 tubes)
03615042	24 - 1.12 mL tubes (6 blisters of 4 tubes)

Profender is protected by the following U.S. Patents: 5 514 773, 5 589 503, and other patents pending.

Made in Germany

NADA #XXX-XXX, Approved by FDA

03615028/03615034/03615042, R.0
April, 2007

Bayer HealthCare

Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 U.S.A.

Profender® Topical Solution
(emodepside/praziquantel)
Multiple Insert
Back

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

N-141275-A-0000-OT

JUN 2 9 2007

Bayer HealthCare LLC
Animal Health Division
Attention: Pam Triplett
Senior Regulatory Affairs Consultant
P.O. Box 390
Shawnee Mission, KS 66201

Re: Request for original approval of PROFENDER Topical Solution

Dear Ms. Triplett:

We approve your original new animal drug application (NADA) for PROFENDER Topical Solution dated May 15, 2007, amended on May 30, 2007, June 4, 2007, and June 8, 2007. Emodepside and praziquantel topical solution is approved for the treatment and control of hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults, and fourth stage larvae), roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), and tapeworm infections caused by *Dipylidium caninum* (adults) and *Taenia taeniaeformis* (adults) in cats. The expiration dating for this drug is 24 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. Any request to change the conditions of this approval may require the submission of a supplemental application.

PROFENDER Topical Solution, as approved in this letter, qualifies for THREE years of marketing exclusivity beginning as of the date of this letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. §360b(c)(2)(F)(ii)).

Your final printed labeling should be identical to the facsimile labeling submitted May 15, 2007 (A-0000), for the tube labels, blister packs, and shipping labels, June 4, 2007 (M-0002), for the display cartons, and June 8, 2007 (M-0003), for the package insert. You should submit three copies of each component of the final printed labeling to CVM before distributing and marketing the drug product.

Under good manufacturing practices (GMPs) (21 CFR Parts 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the

drug product. A product that does not conform to GMPs is adulterated under section 501(a)(1)(B) of the act (21 U.S.C. §351(a)(1)(B)).

If you submit correspondence relating to this approval, you should reference this letter by date and the alphanumeric identifier found at the top of this letter. If you have any questions, please contact Dr. Melanie R. Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary

US005514773A

United States Patent [19]

Nishiyama et al.

[11] Patent Number: 5,514,773

[45] Date of Patent: May 7, 1996

[54] **DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF**

[75] Inventors: **Hitoshi Nishiyama**, Neyagawa; **Masaru Ohgaki**, Kobe; **Ryo Yamanishi**, Ibaraki; **Toshihiko Hara**, Miura, all of Japan

[73] Assignee: **Fujisawa Pharmaceutical Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **295,782**

[22] PCT Filed: **Mar. 8, 1993**

[86] PCT No.: **PCT/JP93/00286**

§ 371 Date: **Sep. 12, 1994**

§ 102(e) Date: **Sep. 12, 1994**

[87] PCT Pub. No.: **WO93/19053**

PCT Pub. Date: **Sep. 30, 1993**

[30] **Foreign Application Priority Data**

Mar. 17, 1992 [JP] Japan 4-092070
Oct. 15, 1992 [JP] Japan 4-305093

[51] **Int. Cl.**[6] **A61K 38/12**; A61K 38/15; C07K 11/02

[52] **U.S. Cl.** **530/317**; 530/323

[58] **Field of Search** 514/11, 18; 530/323, 530/317; 930/30

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,116,815 5/1992 Takagi et al. 514/11

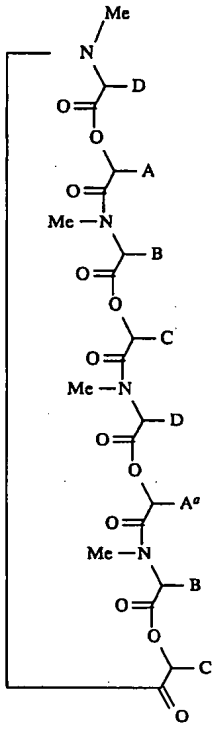
FOREIGN PATENT DOCUMENTS

503538 9/1992 European Pat. Off. .
35796 2/1991 Japan .

Primary Examiner—Jeffrey E. Russel
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

(I)



wherein

A is benzyl group which has suitable substituent(s) or phenyl group which may have suitable substituent(s),

A^a is benzyl group which may have suitable substituent(s) or phenyl group which may have suitable substituent(s),

B and D are each lower alkyl,

C is hydrogen or lower alkyl,

and a pharmaceutically acceptable salt thereof The compound or a salt thereof of the present invention has excellent parasiticidal activities as an anthelmintic agent for animals and human bodies.

12 Claims, No Drawings

DEPSIPEPTIDE DERIVATIVES, PRODUCTION THEREOF AND USE THEREOF

TECHNICAL FIELD

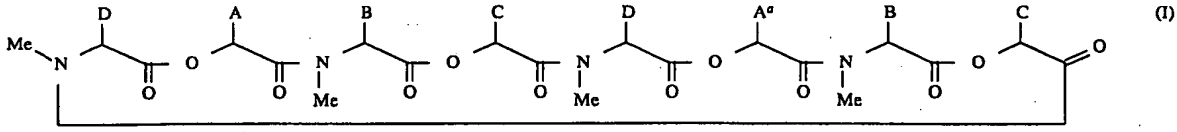
The present invention relates to new depsipeptide derivatives having antiparasitic activity.

BACKGROUND ART

Japanese Kokai Tokkyo Koho 3-35796 discloses depsipeptide derivative prepared by culturing microorganisms.

DISCLOSURE OF INVENTION

The object compound of the present invention, depsipeptide derivatives can be represented by the following general formula (I).



(I)

wherein

A is benzyl group which has suitable substituent(s) or phenyl group which may have suitable substituent(s),

A^a is benzyl group which may have suitable substituent(s) or phenyl group which may have suitable substituent(s),

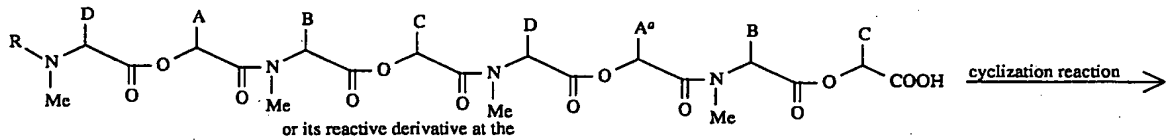
B and D are each lower alkyl,

C is hydrogen or lower alkyl.

According to the present invention, the object compound of depsipeptide derivatives (I) can be prepared by processes which are illustrated in the following schemes.

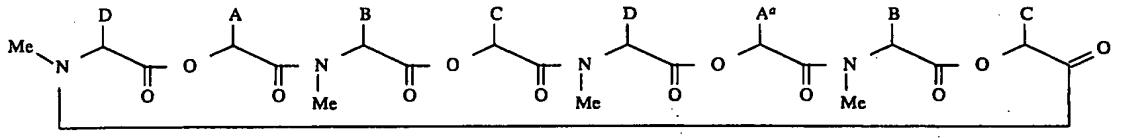
It should be indicated that any of D-configured compound, L-configured compound and/or DL-configured compound are in the extent of the present invention; however, for the convenience, only D-configured compounds and L-configured compounds are explained in the process for preparation as follows.

Process 1



cyclization reaction

or its reactive derivative at the amino or carboxy group or a salt therof

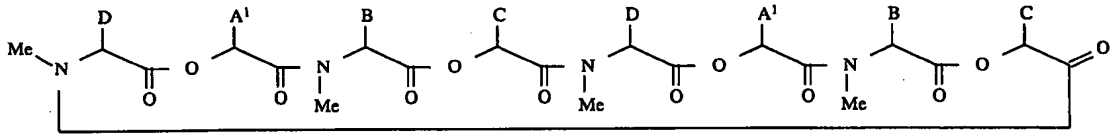


(I)

or a salt thereof

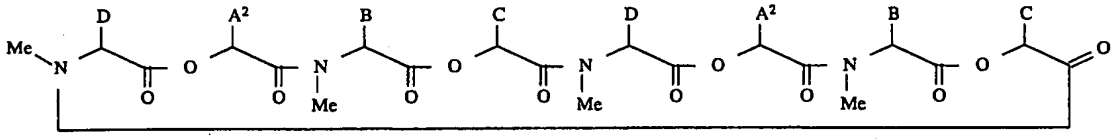
-continued

Process 2



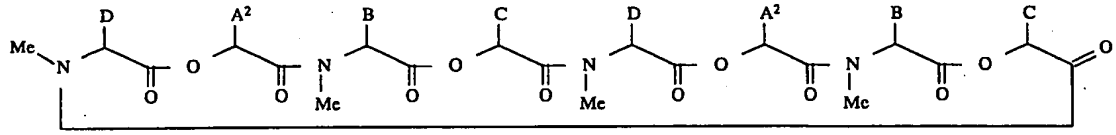
(III)

nitration reaction



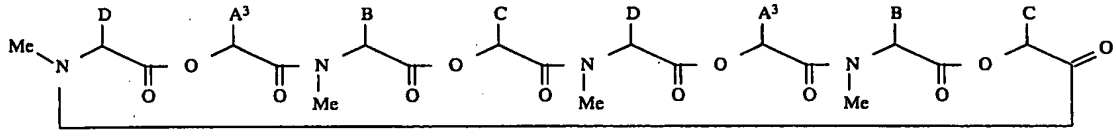
(Ia)

Process 3



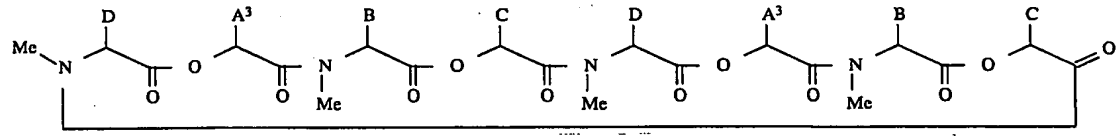
(Ia)

reduction reaction



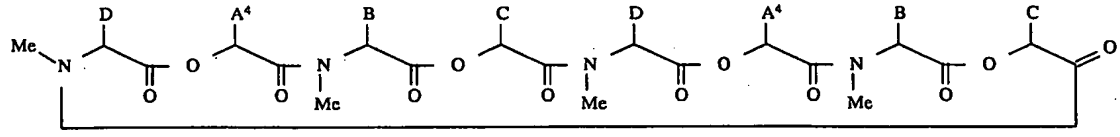
(Ib)

Process 4



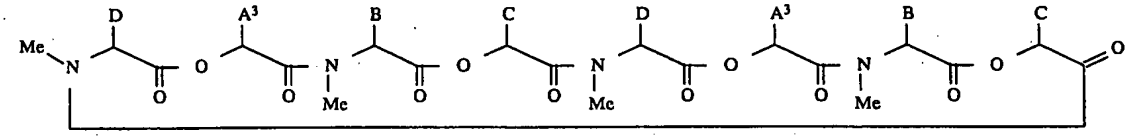
(Ib)

alkylation reaction



(Ic)

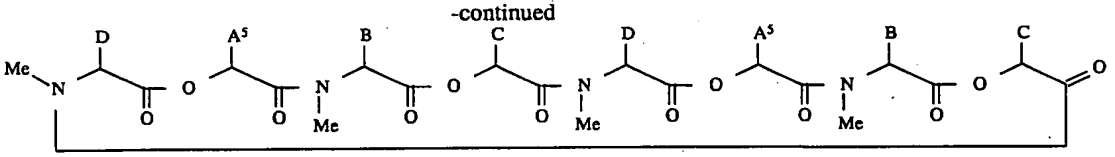
Process 5



(Ib)

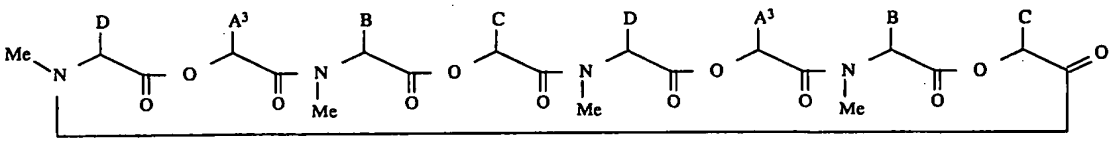
monoalkylation reaction followed by intramolecular alkylation reaction

-continued



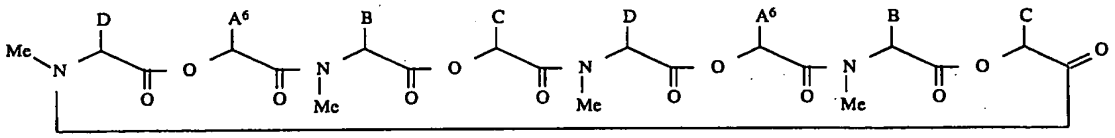
(Id)

Process 6



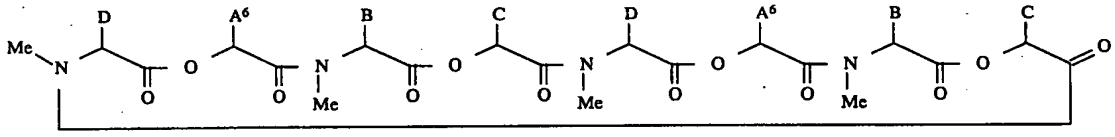
(Ib)

hydroxylation reaction via diazo compound



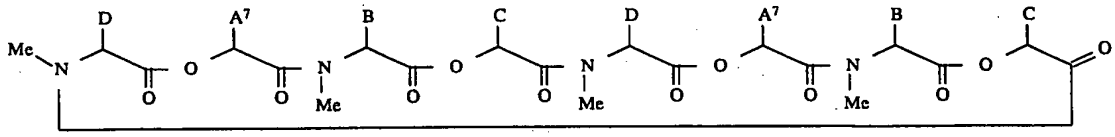
(Ie)

Process 7



(Ic)

alkylation reaction



(If)

wherein

A, A^a, B, C and D are each as defined above,

R is hydrogen or amino protective group,

A^1 is benzyl group which may have lower alkoxy,

A^2 is benzyl group which has nitro, or benzyl group which has nitro and lower alkoxy,

A^3 is benzyl group which has amino, or benzyl group which has amino and lower alkoxy,

A^4 is benzyl group which has mono- or di-lower alkylamino, or benzyl group which has mono- or di-lower alkylamino and lower alkoxy,

A^5 is benzyl group which has cyclic amino, or benzyl group which has cyclic amino and lower alkoxy,

A^6 is benzyl group which has hydroxy, or benzyl group which has hydroxy and lower alkoxy,

A^7 is benzyl group which has lower alkoxy.

Throughout the present specification, the amino acid, peptides, protective groups, condensing agents, etc. are indicated by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be L-configured compounds and residues, and when shown by D- abbreviations, they are meant to be D-configured compounds and residues.

In the present invention, there are employed the following abbreviations.

p-MeOPhLac: 2-hydroxy-3-(4-methoxyphenyl) propionic acid [β-(p-methoxyphenyl)lactic acid]

Man: 2-hydroxyphenylacetic acid [mandelic acid]

p-Me_2NPhLac: 3-(4-dimethylaminophenyl)-2-hydroxypropionic acid [β-(p-dimethylaminophenyl)lactic acid]

p-PipPhLac: 2-hydroxy-3-(4-piperazinophenyl)propionic acid [β-(p-piperazinophenyl)lactic acid]

p-PyrPhLac: 2-hydroxy-3-(4-pyrrolidinophenyl)propionic acid [β-(p-pyrrolidinophenyl)lactic acid

p-NO_2PhLac: 3-(4-nitrophenyl)-2-hydroxypropionic acid [β-(p-nitrophenyl)lactic acid]

p-NH_2PhLac: 3-(4-aminophenyl)-2-hydroxypropionic acid [β-(p-aminophenyl)lactic acid]

p-Et_2NPhLac: 3-(4-diethylaminophenyl)-2-hydroxypropionic acid [β-(p-diethylaminophenyl)lactic acid]

p-Hex_2NPhLac: 3-(4-di-n-hexylaminophenyl)-2-hydroxypropionic acid [β-(p-di-n-hexylaminophenyl)lactic acid]

p-PylPhLac: 2-hydroxy-3-(1H-pyrrol-1-yl-phenyl)propionic acid [β-(p-1H-pyrrol-1-yl)phenyl)lactic acid]

p-OHPhLac: 2-hydroxy-3-(4-hydroxyphenyl)propionic acid [β-(p-hydroxyphenyl)lactic acid]

p-EtOPhLac: 3-(4-ethoxyphenyl)2-hydroxypropionic acid [β-(p-ethoxyphenyl)lactic acid]

p-HexOPhLac: 3-(4-n-hexyloxyphenyl)-2-hydroxypropionic acid [β-(p-n-hexyloxyphenyl)lactic acid]

p-MEPhLac: 2-hydroxy-3-[4-(2-methoxyethoxy)phenyl] propionic acid [β-[p-(2-methoxyethoxy)phenyl]lactic acid]

p-MEEPhLac: 2-hydroxy-3-{4-[2-(2-methoxyethoxy) ethoxy]phenyl}propionic acid [β-{p-[2-(2-methoxyethoxy)ethoxy]phenyl}lactic acid]

o-MeOPhLac: 2-hydroxy-3-(2-methoxyphenyl)propionic acid [β-(o-methoxyphenyl)lactic acid]

m-MeOPhLac: 2-hydroxy-3-(3-methoxyphenyl)propionic acid [β-(m-methoxyphenyl)lactic acid]

3,4-DMOPhLac: 3-(3,4-dimethoxyphenyl)-2-hydroxypropionic acid [β-(3,4-dimethoxyphenyl)lactic acid]

2,4-DMOPhLac: 3-(2,4-dimethoxyphenyl)-2-hydroxypropionic acid [β-(2,4-dimethoxyphenyl)lactic acid]

3,4-MODPhLac: 2-hydroxy-3-(3,4-methylenedioxyphenyl) propionic acid [β-(3,4-methylenedioxyphenyl)lactic acid]

3-MA-4-MOPhLac: 3-(3-dimethylamino-4-methoxyphenyl)-2-hydroxypropionic acid [β-(3-dimethylamino-4-methoxyphenyl)lactic acid]

3,4-DMAPhLac: 3-[(3,4-bis(dimethylamino)phenyl]-2-hydroxyphenyl]propionic acid [β-[3,4-bis(dimethylamino)phenyl]lactic acid]

o-FPhLac: 3-(2-fluorophenyl)-2-hydroxypropionic acid [β-(o-fluorophenyl)lactic acid]

m-FPhLac: 3-(3-fluorophenyl)-2-hydroxypropionic acid [β-(m-fluorophenyl)lactic acid]

p-FPhLac: 3-(4-fluorophenyl)-2-hydroxypropionic acid [β-(p-fluorophenyl)lactic acid]

Glycol: Glycolic acid

PhLac: 2-hydroxy-3-phenylpropionic acid [β-phenyllactic acid]

Lac: 2-hydroxypropionic acid [lactic acid]

p-MorPhLac: 2-hydroxy-3-(4-morpholinophenyl)propionic acid [β-(p-morpholinophenyl)lactic acid]

Suitable salts of the compound (I) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkali earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid,etc.); and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom (s), preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable substituent(s) in the term "benzyl group which has substituent(s)", "phenyl group which may have substituent(s)" and "benzyl group which may have substituent(s)" may include hydroxy, lower alkoxy, lower alkoxy lower alkoxy, lower alkoxy lower alkoxy lower alkoxy, halogen, lower alkyl, amino, cyclic amino, nitro, halogen (e.g. fluoro, chloro, bromo, iodo, etc.) and the like. These may have 1 or more than 2 substituents.

Suitable "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s) such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, isopentyloxy, hexyloxy, and the like.

Suitable "lower alkoxy lower alkoxy" may include methoxymethoxy, methoxyethoxy, methoxypropoxy, ethoxyisopropoxy, and the like.

Suitable "lower alkoxy lower alkoxy lower alkoxy" may include methoxymethoxyethoxy, methoxyethoxyethoxy, methoxyethoxypropoxy, ethoxymethoxyisopropoxy, and the like.

Suitable "cyclic amino group" may be aromatic ring or alicyclic compound which have more than 1 nitrogen atom(s) as hetero atom(s), and it containing monocyclic group or condensed polycyclic group which may be saturated or unsaturated. Also, cyclic amino group may further contain hetero atom(s) such as more than 1 or 2 nitrogen atom(s), oxygen atom(s), sulfur atom(s), and the like and still further the cyclic amino group may be spiro ring or bridged cyclic compound. The number of the constructive atom(s) of cyclic amino group are not limited, but for example, monocyclic group have 3 to 8-membered rings and bicyclic have 7 to 11-membered rings.

Example of such cyclic amino group may include saturated or unsaturated monocyclic group which contain one nitrogen atom as hetero atom(s) such as 1-azetidinyl, pyrrolidino, 2-pyrroline-1-yl, 1-pyrrolyl, piperidino, 1,4-dihydropyrizine-1-yl, 1,2,5,6-tetrahydropyrizine-1-yl, homopiperidino and the like, saturated or unsaturated monocyclic group which contain more than two nitrogen atom(s) as hetero atom(s) such as 1-imidazolidinyl, 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 1-tetrazolyl, 1-piperazinyl, 1-homopiperazinyl, 1,2-dihydropyridazine-1-yl, 1,2-dihydropyrimidine-1-yl, perhydropyrimidine-1-yl, 1,4-diazacyclo heptane-1-yl, saturated or unsaturated monocyclic group which contain 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) as hetero atom(s) such as oxazolidine-3-yl, 2,3-dihydroisooxazole-2-yl, morpholino, saturated or unsaturated monocyclic group which contain 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) as hetero atom(s) such as thiazolidine-3-yl, isothiazoline-2-yl, thiomorpholino, condensed polycyclic group such as indole-1-yl, 1,2-dihydrobenzimidazole-1-yl, perhydropyrrolo[1,2-a]pyrazine-2-yl, spirocyclic group such as 2-azaspiro[4,5]decane-2-yl, bridged cyclic heterocyclic group such as 7-azabicyclo[2,2,1]heptane-7-yl, and the like.

Said lower alkoxy, lower alkyl, amino, cyclic amino group and the like may have suitable substutuent(s), such as lower alkylamino which is mono- or di-substituted, lower alkenyl, aralkyl, aryl, hydroxy, hydroxy lower alkyl, nitro, cyano, above mentioned cyclic amino, above mentioned lower alkoxy, lower alkoxy lower alkyl, halogen, halo lower alkyl, amino, protected amino, amino lower alkyl, protected amino lower alky, cyclo lower alkylamino, and the like.

The numbers of these substituent(s) are not limited, preferably 1 to 4, and the substituent(s) may be the same or not the same. Also two of the same or not the same substituent(s) may substitute the same atom(s) on cyclic amino group.

"Mono- or di-lower alkylamino group" may include amino group which has the group of one or two lower alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl, tert-pentyl, etc.), preferably methylamino, ethylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, dibutylamino, etc.

"Lower alkenyl group" may include vinyl, allyl, isopropenyl, and the like. "Aralkyl group" may include benzyl, 1-phenylethyl, and the like.

"Aryl group" may include phenyl, naphthyl, and the like.

"Hydroxy lower alkyl group, alkoxy lower alkyl group, halo lower alkyl group, amino lower alkyl group, protected amino lower alkyl group" means that optional carbon atom(s) of above mentioned lower alkyl has each hydroxy, alkoxy, halogen, amino, protected amino.

"Amino protecting group", may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, pivaloyl, hexanoyl, etc.), mono- (or di- or tri-) halo (lower) alkanoyl group (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.), lower alkoxycarbonyl group, (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc.), carbamoyl group, aroyl group (e.g. benzoyl, toluoyl, naphthoyl, etc.), ar (lower) alkanoyl group (e.g. phenylacetyl, phenylpropionyl, etc.), aryloxycarbonyl group (e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.), aryloxy (lower) alkanoyl group (e.g. phenoxyacetyl, phenoxypropionyl, etc.), arylglyoxyloyl group, (e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.), ar (lower) alkoxycarbonyl group which may have suitable substituent(s), (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.), ar (lower) alkylidene group which are substituted or not substituted (e.g. benzylidene, hydroxybenzylidene etc.), ar (lower)alkyl group such as mono- (or di- or tri-) phenyl (lower) alkyl (e.g. benzyl, phenethyl, benzhydryl, trityl, etc.) and the like.

Above mentioned amino protective group contain the protective group which have the function to temporarily protect amino group which is often used in the field of amino acid and peptide chemistry.

Suitable "benzyl group which has lower alkoxy" may include lower alkoxy substituted benzyl such as 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 2,3,4-trimethoxybenzyl, 2-ethoxybenzyl, 4-hexyloxybenzyl, etc.

Suitable "benzyl group which has halogen" may include halogen substituted benzyl such as 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2-bromobenzyl, 2-bromo-4-chlorobenzyl, etc.

Suitable "benzyl group which has lower alkyl" may include lower alkyl substituted benzyl such as 4-methylbenzyl, 4-ethylbenzyl, 4-propylbenzyl, 4-isopropylbenzyl, 4-butylbenzyl, 4-isobutylbenzyl, 4-tert-butylbenzyl, 4-pentylbenzyl, 4-hexylbenzyl, 2,3-dimethylbenzyl, 2,6-dimethylbenzyl, 3,4-dimethylbenzyl, 2,4,6-trimethylbenzyl, etc.

Suitable example of phenyl group which have such substituent(s) may include lower alkoxy substituted phenyl group (e.g. 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2-ethoxyphenyl, 4-hexyloxyphenyl, etc.), halogen substituted phenyl (e.g. 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 2-bromophenyl, 2-bromo-4-chlorophenyl, 4-fluorophenyl, 2,4-difluorophenyl etc.), hydroxy substituted phenyl (e.g. 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, etc.), lower alkoxy- and hydroxy-substituted phenyl (e.g. 2-(hydroxymethoxy) phenyl, etc.).

Suitable example of benzyl group which have such substituent(s) may include lower alkoxy substituted benzyl (e.g. 4-methoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 2,3,4-trimethoxybenzyl, 2-ethoxybenzyl, 4-hexyloxybenzyl, etc.), halogen substituted benzyl (e.g. 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2bromobenzyl, 2-bromo-4-chlorobenzyl, etc.), hydroxy substituted benzyl (e.g. 2-hydroxybenzyl, 3-hydroxybenzyl, 4-hydroxybenzyl, etc.), lower alkoxy and hydroxy substituted benzyl (e.g. 2-(hydroxymethoxy) benzyl, etc.)

More preferable example of "cyclic amino group which may have substituent(s)" may include pyrrolidino, morpholino, 1-piperazino, 4-methylpiperazino, piperidino and the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by subjecting the compound (II) or its reactive derivative at the amino group or carboxy group or a salt thereof to cyclization reaction.

The starting compound (II), its reactive derivative or a salt thereof is new and such compounds can be prepared by the methods described in Preparation mentioned below or in substantially the same manner.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as a aliphatic carboxylic acid [e.g. acetic acid, propionic acid, burytic acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride, and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used. The reaction is usually carried out in the usual method which is used in cyclization reaction, under heating or in the presence of a conventional condensing agent. When R in the compound (II) is amino protective group, the elimination of the amino protective group is carried out previous to ring cyclization reaction.

Suitable condensing agent may include carbodiimide or a salt thereof [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or hydrochloride thereof, diphenyl phosphoryl azide, diethyl phosphorocyanidate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, etc.]; N,N'-carbonyldiimidazole, N,N'-carbonylbis-(2-methylimidazole); keteneimine compound(e.g. pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylen; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thionyl chloride; oxalyl chloride; combining triphenylphosphine, and carbon tetrachloride or siazen carboxylate; 2-ethyl-7-hydroxybenzisoxazolium salt;

2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 1-hydroxybenzotriazol; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction in the presence of conventional condensing agent may be carried out in an organic solvent such as dichloromethane, methanol, ethanol, propanol, acetonitrile, pyridine, N,N-diethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, benzene, toluene, xylene, etc. or any other solvent mixture which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. Further, ring cyclization reaction under heating can be carried out to heat under boiling point in the solvent which is used in an organic solvent as above.

Process 2

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (III) or a salt thereof to nitration reaction.

The starting compounds (III) contain known compounds (Japanese Kokai Tokkyo Koho No. 3-35796) and novel compounds. The novel compounds can be prepared by the procedures described in Preparations and Examples mentioned later or in substantially the same manner.

This reaction is carried out by reacting the compound (III) or a salt thereof with nitration agent (e.g. nitric acid, etc.).

The reaction can usually be carried out in a conventional solvent such as dichloromethane which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

This reaction can be carried out in substantially the same manner as Example 7 mentioned later.

Process 3

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to the reduction reaction.

This reaction can be carried out in a conventional manner for reducing: nitro to amino, and it may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.]. palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The object compound (Ic) or a salt thereof can be prepared by subjecting the isolated or not isolated the compound (Ib) or a salt thereof, which is obtained by the Process 3, to alkylation reaction. This reaction can be carried out by combining aldehyde and reduction agent or alkylhalide and base. Suitable reduction agents are metallic hydride complex compound, [e.g. sodium borohydride, sodium cyanoborohydride, potassium borohydride, bis(2-methoxyethoxy) aluminium hydride, etc.], a combination of hydrogen, formic acid, or ammonium formate, and palladium catalysts [e.g. palladium on carbon, palladium hydroxide on carbon, palladium black, etc.].

Suitable base may include an inorganic base such as sodium bicarbonate, potassium carbonate, etc., or an organic base such as pyridine, triethylamine, etc. The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction. The reaction which is combined by aldehyde and reduction agents can be carried out in substantially the same manner as Preparation 23 or Example 8 mentioned later, and the reaction which is combined by an alkyl halide and a base can be carried out in substantially the same manner as Preparation 41 mentioned later.

The reaction which is combined by the compound containing two aldehydes and reduction agents can be carried out in substantially the same manner as Example 31 mentioned later.

Process 5

The object compound (Id) or a salt thereof can be prepared by subjecting the isolated or not isolated compound (Ib) or a salt thereof, which is obtained by the Process 3, to mono alkylation reaction followed by intramolecular alkylation reaction. The reaction can be carried out by combining a compound, which has two aldehydes in the molecule, and reduction agents or by combining a compound, which has two halogens and a base.

Process 6

The object compound (Ie) or a salt thereof can be prepared by subjecting the isolated or not isolated object compound (Ib) or a salt thereof, which is obtained by the Process 3, to hydroxylation reaction by diazotization reaction followed by decomposition of diazonium salt. This reaction can be carried out by reacting the compound (Ib) or a salt thereof with sodium nitrite in the presence of an inorganic or an organic acid and decomposing a growing diazonium salt in water or an organic acid under the room temperature to heating, carrying out hydrolysis if necessary. It is possible to prepare the compound (Ie) or a salt thereof by transforming the amino group of the compound (Ib) or a salt thereof into a hydroxyl group. Suitable acid may include an inorganic acid [e.g. sulfuric acid, hydrochloric acid, borofluoric acid, etc.], and an organic acid [e.g. acetic acid, trifluoroacetic acid, etc.].

Process 7

The object compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt, which is obtained by the Process 6, thereof to alkylation reaction. This reaction can be prepared by combining a alkylhalide and a base.

The reaction can be carried out substantially in the same manner as the later mentioned Example 15 and Example 16.

Suitable base may include an inorganic base [e.g. sodium bicarbonate, potassium carbonate, etc. and an organic base [e.g. pyridine, triethylamine, etc.].

The compound or its salt of the present invention has excellent parasiticidal activities as an anthelmintic agent for animals and human bodies. It is effective to nematodes which are infected particularly to the domestic animals, domestic fowls or pets such as pigs, sheep, goats, cattle, horses, dogs, cats, and chickens.

Haemonchus genus, Trichostrongylus genus, Ostertagia genus, Nematodirus genus, Cooperia genus, Ascaris genus, Bunostomum genus, Oesophagostomum genus, Chabertia genus, Trichuris genus, Strongylus genus, Trichonema genus, Dictyocaulus genus, Capillaria genus, Heterakis genus, Toxocara genus, Ascaridia genus, Oxyuris genus, Ancylostoma genus, Uncinaria genus, Toxascaris genus, Parascaris genus, Nippostrongylus genus, Metastrongylus genus, Hyostrongylus genus, Strongyloides genus, Cyathostomum genus.

The parasiticidal activities are pointed out in some kind of Nematodirus genus, Cooperia genus, and Oesophagostomum genus which attack the intestinal tract, however, just Haemonchus genus and Ostertagia genus are parasitic on the stomach, and parasites of Dictyocaulus genus are found in lungs.

The parasites of Filariidae or Setariidae activities are found in heart and blood vessels, hypodermis, or lymphatic vessel or any other organisms or organs.

It is also effective to parasites which infect human beings. The most common parasites in the alimentary canal of human beings are as follows:

Ancylostoma genus, Necator genus, Ascaris genus, Strongyloides genus, Tichinell genus, Capillaria genus, Trichuris genus, and Enterobius genus.

It is also active for other medically important parasites, which is found in the blood or other organisms or organs out side of the alimentary canal, such as Wuchereria genus, Brugia genus, Onchocerca genus and Loa genus in Filariidae, as well as parasites such as Dracunlus genus in Dracunculidae. It is also active for parasites such as Strongyloides genus and Trichinella genus in the intestinal tract in a particular conditioned parasitism out side of intestinal tract.

Test

Test 1

(1) Test Compounds

The compounds which are illustrated in Example 1, Example 3, Example 4, Example 5, Example 10, Example 17, Example 23, Example 24, Example 25, and Example 29.

(2) Test

The effect of parasiticides was examined with the rats which was infected by nematodes which are parasitic on rats, *Nippostrongylus brasilienses.*

Wistar strain rats (female 6 weeks old, 120–130 g weight) were sacrificed by infecting them and giving them subcutaneous injections of 3000 infective larvae per rat.

Test compound of 50 mg was dissolved in 0.25 ml dimethylsulfoxide, 0.5% methylcellulose solution was added, and liquid volume was adjusted to be prescribed volume of 100, 10, 5, 2.5, 1.25, 1.0, 0.63, 0.32 mg/kg to utilize. After they were infected, on each 7th, 8th, and 9th day, the test compound was administered orally with above concentration. On the 11th day, the rat was dissected and the numbers of parasites in the small intestines were measured.

The given measurement was based to calculate the reduction rate from the percentage of the numbers of the parasites of unadministered rats (control). The result of it is shown in the

Test 2

The reduction rate was calculated in a similar manner as Test 1 except when the test compound was subcutaneously administered to the rats instead of oral administration as in Test 1. The result of that is shown in the Table 2.

Test 3

For 1 rat, the 5000 infective larvae of *Strongyloides venezuelensis* were infected percutaneously to one group (2 rats) of 8 weeks old Mongolian gerbils. On the 10th day after they were infected, the suspended test compound was orally administered once with the amount of established administration. The effect was judged according to the amount of the eggs in the feces or the numbers of worms in the intestinal tract. The measurement of the numbers of the eggs were taken from O ring method, and the numbers of the eggs (EPG) in 1 g of feces were counted on the day before, on the day, and on the 1st, 2nd, 3rd, and 4th day after the administration. The numbers of the parasites were measured by dissecting Mongolian gerbils the 4th day after the administration (on the 14th day after infection). The method of measurement was followed by releasing the parasites, which live in the small intestines, into saline solution over night, and the released parasites were set to be as numbers of worms recovered.

The result (the mean number of each group) is shown in the Table 3.

Test Results

TABLE 1

Test Compounds	Minimum Amount of Administration indicated by more than 95% of Reduction Rate
PF1022 (Japanese Patent Application 3 - 35796)	10 mg/kg
Example - 1	2.5 mg/kg
Example - 3	1.25 mg/kg
Example - 4	2.5 mg/kg
Example - 5	0.63 mg/kg
Example - 10	2.5 mg/kg
Example - 17	2.5 mg/kg
Example - 23	5 mg/kg
Example - 24	5 mg/kg
Example - 25	5 mg/kg
Example - 29	5 mg/kg

TABLE 2

Test Compounds	Minimum Amount of Administration indicated by more than 95% of Reduction Rate
PF1022 (Japanese Patent Application 3 - 35796)	>100 mg/kg
Example - 1	10 mg/kg
Example - 3	5 mg/kg
Example - 5	1.25 mg/kg
Example - 12	50 mg/kg

TABLE 3

Test Compounds	Dose	Change in Numbers of Parasites' Number of Eggs in Feces (EPG/100) −2	0*	1	2	3	4	Numbers of the Worms recovered
Unadministered control	—	574	1240	1725	2343	1533	1505	3005
PF1022	20 mg/kg	332	1615	581	1563	935	1005	3088
Example-5	5 mg/kg	455	1890	701	0	0	0	0
Example-5	2.5 mg/kg	838	1665	452	0	0	0	0
Example-5	1.25 mg/kg	551	2800	536	0	0	30	8

*stands for the starting day of administration.

When the compound of the present invention are used for animals and human being as an anthelmintic agent, it can be administered orally as a liquid drink. The liquid drink is usually suspended agent such as bentonite, and wetting agent, or other excipients with non-toxic solution, or solution made of water, suspension, or dispersed solution, and generally it comprises liquid drinks or antifoaming agent. The prescription of a liquid drink contains generally activated compound for 0.01–0.5 weight %, preferably 0.0–0.1 weight %. When it is preferably administered orally as a dried solid single dose, capsules, pills, or tablets, which comprise the desired amount of activated compounds are usually used. These forms of dosage are prepared by homogeneous admixtures of diluent, filler, disintegrator and/or excipient agents such as dextrine, lactose, talc, magnesium stearate, vegetable rubber, etc.

The usage of such single dose prescription can be varied broadly by kind of hosts, or kind of parasites, or weight of hosts which are to be treated and referring to the weight and containing quantity of anthelmintics.

When it is administered in animal feed, it is used as to disperse homogeneously, or as top dressing, or in the form of pellet. To achieve preferable effect of antiparasites, the activated compound of 0.0001–2% is usually contained in feed.

The dosage which was dissolved or dispersed in liquid carrier excipients can be administered to animals parenterally by giving them injections in the anterior stomach, muscle, tachea, or under the skin. The activated compound is mixed with suitable vegetable oil such as peanut oil or cottonseed oil for parenteral administration. These prescriptions generally contain the activated compound of 0.05–50 weight %. It can also be administered locally by mixing in a suitable carrier such as dimethylsulfoxide or hydrocarbon solvent. The prepared solvents can be used directly on the exterior of animals by sprays or direct injections.

The most suitable usage amount of the activated compound to achieve the most effective result depends on the kind of animals, which are to be treated, and type of parasital infection and its stage. It can be achieved by oral administration of the activated compound 0.01–100 mg, preferably 0.5–50.0 mg, per kg of the treated animal. Such dosage amount is given in a relatively short term of 1–5 days at once or separately.

The Preparations and Examples of the present invention are shown in the following.

Preparation 1

Boc-Tyr (Me)-OH (5.1 g), was dissolved in 4N-hydrogen chloride in dioxane (87.5 ml) and stirred under ice-cooling for 2 hours. After dioxane was evaporated in vacuo, the residue was dissolved in 6N-hydrochloric acid aqueous solution (45 ml) and at 0° C., sodium nitrite (1.9 g) was added by portions. After stirring for 4 hours, the reaction solution was extracted with ether (100 ml×3). After washing ether layer by saturated brine, the extract was dried over calcium chloride and the solvent was evaporated in vacuo. To the residue, benzene (30 ml), benzyl alcohol (3.4 ml) and p-toluenesulfonic acid mono hydrate (0.22 g) were added and heated under reflux for 3 hours by using Dean Stark apparatus. After cooling down to the room temperature, the crude product, which was gained by evaporating the solvent, was purified by silica gel chromatography (eluting with ethyl acetate: hexane=1:10, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate (1.79 g).

NMR ($CDCl_3$, δ): 3.12 (dd,1H), 3.29 (dd,1H), 3.78 (s,3H), 4.44 (t, 1H), 5.07–5.25 (m,2H), 6.77–7.36 (m,9H).

Preparation 2

To a solution of Boc-MeLeu-OH (1.37 g) in methanol (30 ml) and water (10 ml) was added 20% aqueous cesium carbonate solution to be pH7.0. After the solvent was evaporated in vacuo, azeotroped three times by toluene (10 ml). The residue was dissolved in dimethylformamide (20 ml), under ice-cooling, benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate (1.79) was added and stirred at room temperature for 24 hours. The reaction solution was poured into water (150 ml), extracted with ether (100 ml×3), washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:8, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-OBzl (1.59 g).

NMR ($CDCl_3$,δ): 0.90 (d,6H), 1.41 (s) and 1.49 (s) (9H), 1.40–1.58 (m, 3H), 2.62–2.67 (m,3H), 3.06–3.15 (m,2H), 3.77 (s,3H), 4.68–4.80 (m) and, 4.97–5.29 (m) (4H), 6.78 (d,2H), 7.06 (d,2H), 7.26–7.36 (m,5H).

Preparation 3

To a solution of Boc-MeLeu-D-p-MeOPhLac-OBzl (1.36 g) in methanol (15 ml) was added 10% palladium on carbon (0.4 g), and hydrogenated at atmospheric pressure of hydrogen gas for 45 minutes at ambient temperature. The catalyst

was filtered off, the solvent was evaporated to give Boc-MeLeu-D-p-MeOPhLac-OH (1.08 g).

NMR ($CDCl_3$,δ): 0.89–0.95 (m,6H), 1.44 (s,9H), 1.44–1.79 (m,3H), 2.66–2.82 (m,3H), 3.01–3.20 (m,2H), 3.79 (s,3H), 4.40–4.75 (m,1H),5.15–5.38 (m,1H), 6.82 (d,2H), 7.14 (d,2H).

Preparation 4

Boc-MeLeu-D-Lac-OBzl (1.04 g) was dissolved in 4N-hydrogen chloride in dioxane (12.5 ml), under ice-cooling stirred for 3 hours. After the solvent was evaporated in vacuo, azeotroped twice by toluene (10 ml) to give H-MeLeu-D-Lac-OBzl.HCl (1g).

NMR ($CDCl_3$, δ): 0.94–1.00 (m,6H), 1.59 (d,3H), 1.78–2.13 (m,3H), 2.62–2.75 (m,3H), 3.78–3.85 (m,1H), 5.09–5.29 (m,3H), 7.25–7.43 (m,5H), 9.80–10.00 (m,1H), 10.30–10.55 (m,1H).

Preparation 5

To the mixture of Boc-MeLeu-D-pMeOPhLac-OH (1g), H-MeLeu-D-Lac-OBzl.HCl (1 g) in dichloromethane (20 ml) and triethylamine (15 ml) was added bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.98 g), and was stirred for 13 hours. The water (50 ml) was added to the mixture and it was extracted with ethyl acetate (50 ml×3). After it was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (1.59 g).

NMR ($CDCl_3$,δ): 0.80–0.99 (m,12H), 1.42–1.80 (m,18H),2.66–3.04 (m,8H), 3.78 (s,3H), 4.64–5.43 (m,6H), 6.81 (d,2H), 7.12–7.39 (m,7H).

Preparation 6

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl was used instead of Boc-MeLeu-D-p-MeOPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.67 g) was obtained according to a similar manner to that of

Preparation 3.

NMR ($CDCl_3$,δ): 0.82–0.94 (m,12H), 1.46 (s,9H), 1.40–1.80 (m,9H), 2.67–3.29 (m,8H), 3.77 (s,3H), 4.83–5.71 (m,4H), 6.80 (d,2H), 7.15 (d,2H).

Preparation 7

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.75 g) was dissolved in 4N-hydrogen chloride in ethyl acetate (5.25 ml), and it was stirred under ice-cooling for three hours. After the solvent was evaporated in vacuo, it was azeotroped twice by toluene (10 ml) to give H-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl.HCl (0.74 g).

NMR ($CDCl_3$,δ): 0.77–1.00 (m,12H), 1.21–1.98 (m,9H), 2.61–3.10 (m,8H),3.77 (s,3H), 3.62–3.82 (m,1H), 5.04–5.55 (m,6H), 6.83 (d,2H). 7.12–7.34 (m,7H), 9.30–9.50 (m,1H), 10.40–10.59 (m,1H).

Preparation 8

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.67 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl.HCl (0.74 g) was used instead of H-MeLeu-D-Lac-OBzl.HCl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.80–0.99 (m,24H), 1.10–1.70 (m,2.7H), 2.65–3.10 (m,16H), 3.77 (s,6H), 4.61–5.49 (m,10H), 6.78–6.85 (m,4H), 7,12–7.40 (m,9H).

Preparation 9

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl (0.92 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-pMeOPhLac-MeLeu-D-Lac-OH (0.89 g) was obtained according to a similar manner to that of Preparation 3.

NMR ($CDCl_3$,δ): 0.79–0.99 (m,24H), 1.10–1.80 (m,2.7H), 2.65–3.10 (m,16H),3.77 (s,6H), 4.60–5.65 (m,8H), 6.78–6.90 (m,4H),7.13–7.25 (m,4H).

Preparation 10

To a solution of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH (0.89 g) and pentafluorophenol (0.14 g) in dichloromethane (10 ml) were added under ice-cooling, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride (0.22 g), and stirred for 3 hours. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-pMeOPhLac-MeLeu-D-Lac-OC_6F_5 (0.8 g).

NMR ($CDCl_3$,δ): 0.80–0.99 (m,24H), 1.10–1.80 (m,2.7H), 2.65–3.18 (m,16H),3.77 (s,6H), 4.60–5.55 (m,8H), 6.78–6.90 (m,4H), 7.10–7.22 (m,4H).

Preparation 11

To a solution of H-D-Man-OH (1 g) and triethylamine (0.92 ml) in ethyl acetate (50 ml) was added phenacyl bromide (1.31 g) under ice-cooling. After the mixture was stirred for 48 hours at room temperature, the reaction mixture was poured into water and was extracted with ethyl acetate (50 ml×3). After the extract was dried over anhydrous magnesium sulfate, it was concentrated in vacuo to give H-D-Man-OPac (1.7 g).

NMR ($CDCl_3$,δ): 5.30 (d,1H), 5.41 (s,1H), 5.47 (d,1H), 7.31–7.88 (m,10H).

Preparation 12

To a solution of Boc-MeLeu-OH (1.54 g), and H-D-Man-OPac (1.7 g) in methylene chloride (50 ml) were added dimethylaminopyridine (77mg) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.hydrochloride (1.32 g) under ice-cooling, The mixture was stirred for 3 hours successively. After methylene chloride was evaporated in vacuo, ethyl acetate (200 ml) was added, and washed with water, the solution was dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-Man-OPac (3 g).

NMR ($CDCl_3$,δ): 0.91–0.97 (m,6H), 1.39 (s) and 1.43 (s) (9H),1.40–1.86 (m,3H), 2.85 (s) and 2.88 (s) (3H), 4.80–4.88 (m) and 5.04–5.12 (m) (1H), 5.29 (d,1H), 5.40 (d,1H),6.11 (s) and 6.15 (s) (1H), 7.40–7.86 (m,10H).

Preparation 13

To 90% aqueous acetic acid (30 ml) of Boc-MeLeu-D-Man-OPac (3 g) was added zinc powder (3 g) and stirred for 1 hour at room temperature. After filtering the zinc residue, the solvent was evaporated in vacuo. Ethyl acetate (200 ml) was added to the residue, and washed with 10% aqueous citric acid, water, and saturated brine. After drying over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of methylene chloride, ethanol and acetic acid (20:1:0.1, v/v). The frac-

tions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-Man-OH (2.22 g).

NMR ($CDCl_3$,δ): 0.91–0.97 (m,6H), 1.28 (s) and 1.44 (s) (9H),1.40–1.80 (m,3H), 2.86 (s,3H), 4.80–4.98 (m,1H), 5.95 (s,1H), 7.39–7.50 (m,5H).

Preparation 14

Trichloroethyl (S)-2-chloropropionate (4.8 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-Lac-OTce (7.98 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.93–0.98 (m,6H), 1.47 (s,9H), 1.59 (d,3H), 1.50–1.78 (m,3H), 2.81 (s) and 2.84 (s) (3H), 4.64–5.05 (m,3H), 5.19 (q,1H).

Preparation 15

Boc-MeLeu-D-Lac-OTce (2.7 g) was used instead of Boc-MeLeu-D-Lac-OBzl. Except above matter, H-MeLeu-D-Lac-OTce.HCl (2.45 g) was obtained according to a similar manner to that of Preparation 4.

NMR ($CDCl_3$,δ): 0.95–1.03 (m,6H), 1.68 (d,3H), 1.80–2.16 (m,3H), 2.74–2.80 (m,3H), 3.80–3.99 (m,1H), 4.67 (d,1H), 4.96 (d,1H), 5.32 (q,1H), 9.80–10.10 (m,1H), 10.30–10.60 (m,1H).

Preparation 16

Boc-MeLeu-D-Man-OH (2.22 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-Lac-OTce-.HCl (2.4 g) was used instead of H-MeLeu-D-Lac-OBzl-.HCl. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (3.33 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.77–0.99 (m,12H), 1.35 (s,9H), 1.26–1.84 (m,9H), 2.79–2.98 (m,6H), 4.53–5.55 (m,5H), 6.15–6.24 (m,1H), 7.39–7.46 (m,5H).

Preparation 17

Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.5 g) was used instead of Boc-MeLeu-D-Man-OPac. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OH (1.46 g) was obtained according to a similar manner to that of Preparation 13.

NMR ($CDCl_3$,δ): 0.79–0.99 (m,12H), 1.37 (s,9H), 1.20–1.83 (m,9H), 2.79–2.96 (m,6H), 4.53–5.40 (m,3H), 6.14–6.26 (m,1H), 7.39–7.44 (m,5H).

Preparation 18

Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.5 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OBzl. Except above matter, H-MeLeu-D-Man-MeLeu-D-Lac-OTce.HCl (1.3 g) was obtained according to a similar manner to that of Preparation 7.

NMR ($CDCl_3$,δ): 0.78–0.98 (m,12H), 1.30–2.24 (m,9H), 2.78–2.97 (m.6H), 3.79–3.99 (m,1H), 4.52–5.56 (m,4H), 6.27–6.31 (m,1H),7.40–7.52 (m,5H), 9.52–9.90 (m,1H), 10.10–10.42 (m,1H).

Preparation 19

Boc-MeLeu-D-Man-MeLeu-D-Lac-OH (1.4 g) was used instead of Boc-MeLeu-D-p-MeOPhLac-OH. H-MeLeu-D-Man-MeLeu-D-Lac-OTce.HCl (1.3 g) was used instead of H-MeLeu-D-Lac-OBzl.HCl. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-OTce (1.7 g) was obtained according to a similar manner to that of Preparation 5.

NMR ($CDCl_3$,δ): 0.76–1.18 (m,24H), 1.21–1.98 (m,2.7H), 2.79–3.10 (m,12H), 4.52–5.59 (m,8H), 6.13–6.25 (m,2H), 7.15–7.55 (m,10H).

Preparation 20

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OTce was used instead of Boc-MeLeu-D Man-OPac. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OH (1.07 g) was obtained according to a similar manner to that of Preparation 13.

NMR ($CDCl_3$,δ): 0.70–1.10 (m,24H), 1.35 (s,9H), 1.25–1.98 (m,18H), 2.78–3.09 (m,12H), 4.20–5.59 (m,6H), 6.10–6.37 (m,2H), 7.26–7.59 (m,10H).

Preparation 21

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OH was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OH. Except above matter, Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OC_6F_5 (0.96 g) was obtained according to a similar manner to that of Preparation 10.

NMR ($CDCl_3$,δ): 0.72–1.00 (m,24H), 1.10–1.95 (m,2.7H), 2.77–3.09 (m,12H), 4.40–5.68 (m,6H), 6.12–6.24 (m,2H), 7.22–7.58 (m,10H).

Preparation 22

To a solution of ethyl (R)-2-acetoxy-3-(4-nitrophenyl) propionate (5.62 g) in ethanol (50 ml) were added concentrated hydrochloric acid (2.5 ml) and 10% palladium on carbon (0.6 g). The mixture was hydrogenated under atmospheric pressure of hydrogen gas for 3 hours at room temperature. The catalyst was filtered off and the solvent was evaporated in vacuo. To the residue was added 0.05N hydrochloric acid (200 ml) and washed with ether (100 ml×2). Saturated aqueous sodium hydrogencarbonate was added to water layer until pH10, and extracted with ether (100 ml×4). After the ether layer was washed with saturated brine, it was dried over anhydrous magnesium sulfate and evaporated in vacuo. To the residue, benzene (40 ml), benzylalcohol (21 ml) and p-toluenesulfonic acid-mono hydrate (4.76 g) were added, and the mixture was heated under reflux for 4 hours. After ice-cooling down to room temperature, the solvent was evaporated in vacuo. To the residue was added water (200 ml) and washed with ether (100 ml×2). Saturated aqueous sodium hydrogencarbonate was added to water layer until pH10, extracted with ether (100 ml×4). After the ether layer was washed with saturated brine, it was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo to give benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (2.84 g).

NMR ($CDCl_3$,δ) 2.85 (dd,1H),2.6–3.6 (m,3H),3.00 (dd, 1H),4.38 (dd,1H), 5.15 (s,2H),6.53 (d,2H),6.90 (d,2H), 7.25–7.4 (m,5H)

IR (neat): 1740 cm^{-1}

Preparation 23

To a solution of benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (0.26 g) in acetic acid (6 ml) was added paraformaldehyde (0.3 g), and further sodium cyanoborohydride (0.3 g) was added gradually, and stirred for 3 hours. To the solution of sodium bicarbonate (25 ml) and ice (25 g) was added reaction mixture gradually and was extracted with ethyl acetate (50 ml×2). After washing the ethyl acetate layer with saturated brine, it was dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-3(4-dimethylaminophenyl)-2-hydroxypropionate (0.22 g). NMR ($CDCl_3$,δ) 2.64 (d,1H),2.91 (s,6H), 2.90 (dd,1H),3.04 (dd,1H),4.43 (ddd,1H), 5.18 (s,2H),6.63 (d,2H),7.01 (d,2H),7.35 (bs,5H)

IR (neat): 1733, 1612 cm^{-1}

Preparation 24

To a solution of Boc-MeLeu-OH (1.27 g), H-D-p-Me_2NPhLac-OBzl (1.47 g) in methylene chloride (20 ml)

were added under ice-cooling, dimethylaminopyridine (0.15 g), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride (1.01 g), and stirred for 15 hours successively. The solvent was evaporated in vacuo. The water (50 ml) was added to residue and extracted with ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to give Boc-MeLeu-D-p-Me_2NPhLac-OBzl (1.69 g).

NMR ($CDCl_3$,δ) 0.90 (d,6H),1.4–1.65 (m,12H),2.63 (s) and 2.68 (s) (3H),2.93 (s,6H),3.05–3.15 (m,6H),4.65–4.80 (m) and 4.95–5.20 (m) (4H),6.62 (d,2H),7.03 (d,2H),7.1–7.2 (m,5H)

IR (KBr): 1747,1730,1693,1675, cm^{-1}

Preparation 25

To a solution of Boc-MeLeu-D-p-Me_2NPhLac-OBzl (1.67 g) in methanol (30 ml) and tetrahydrofuran (5 ml) was added 10% palladium on carbon (0.3 g), and hydrogenation was done in hydrogen gas under atmospheric pressure for 1 and 0.5 hour. After catalyst was filtrated, the solvent was evaporated in vacuo to give Boc-MeLeu-D-p-Me_2NPhLac-OH (1.44 g).

IR (KBr): 1741,1694 cm^{-1}

Preparation 26

To a mixture of Boc-MeLeu-D-p-Me_2NPhLac-OH (1.44 g) in triethylamine (1.92 ml) and dichloromethane (15 ml) was added under ice-cooling, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.30 g) and stirred successively for 15 and ½ hours. The solvent was evaporated in vacuo, and water (50 ml) was added and extracted with ethyl acetate (50 ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (1.55 g).

NMR ($CDCl_3$,δ) 0.8–1.0 (m,12H),1.4–1.7 (m,18H), 2.7–3.1 (m,8H),2.90 (s,6H),5.65–6.5 (m,6H),6.65 (d,2H), 7.08 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1663 cm^{-1}

Preparation 27

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.77 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (637 mg) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1694,1663 cm^{-1}

Preparation 28

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (765 mg) was dissolved in 4N hydrogen chloride in ethyl acetate (5 ml), and stirred for 2 hours at room temperature. After the solvent was evaporated in vacuo, it was azeotroped twice with toluene (10 ml) to obtain 2HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (783 mg)

IR (KBr): 1744,1647 cm^{-1}

Preparation 29

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.78 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.88 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.75–1.0 (m,24H),1.2–1.8 (m,2.7H), 2.65–3.1 (m,16H), 2.91 (s,12H),4.65–5.5 (m,10H),6.6–6.75 (m,4H),7.0-7.15 (m,4H),7.3–7.7 (m,5H)

IR (KBr): 1740,1694,1662 cm^{-1}

FAB-MS: 1243 $[M+H]^+$

Preparation 30

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl (0.87 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1735,1695,1662 cm^{-1}

Preparation 31

Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.81 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.826 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1743,1646 cm^{-1}

Preparation 32

The suspended solution of benzyl R)-3-(4-aminophenyl)-2-hydroxypropionate (0.27 g), bis(2-chloroethyl)ether (0.12 ml), potassium carbonate (0.28 g), and sodium iodide (0.075 g) in dimethylformamide (1 ml) were heated at 70°–90° C. for 7 hours. After cooling it down to room temperature, water (50 ml) was added and extracted with ether (25 ml×3). After the ether layer was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane, ethyl acetate and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-morpholinophenyl)propionate (0.14 g)

NMR ($CDCl_3$,δ) 2.66 (d,1H),2.91 (dd,1H),3.05 (dd,1H), 3.0–3.15 (m,4H), 3.8–3.95 (m,4H),4.45 (ddd,1H),5.18 (s,2H),6.79 (d,2H),7.05 (d,2H),7.3–7.4 (m,5H)

IR (neat): 1734 cm^{-1}

EI-MS: 341 $[M]^+$

Preparation 33

H-D-p-MorPhLac-OBzl (0.90 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.36 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ) 0.9 (d,6H),1.4–1.65 (m,12H),2.63 (s) and 2.66 (s) (3H), 3.05–3.2 (m,6H),3.85–3.95 (m,4H), 4.7–4.8 (m) and 4.95–5.25 (m) (4H),6.80 (d,2H),7.07 (d,2H),7.1–7.2 (m,5H)

IR (KBr): 1740,1695 cm^{-1}

Preparation 34

Boc-MeLeu-D-p-MorPhLac-OBzl (1.35 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-OH (1.08 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1742,1695 cm^{-1}

Preparation 35

Boc-MeLeu-D-p-MorPhLac-OH (1.08 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above

matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.49 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ) 0.85–0.95 (m,12H),1.4–1.7 (m,18H), 2.78 (s),2.81 (s) and 2.88 (s) (6H),3.0–3.1 (m,2H),3.1–3.15 (m,4H),3.85–3.9 (m,4H),4.65–4.75 (m) and 4.9–5.5 (m) (6H),6.82 (d,2H),7.13 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1662 cm^{-1}

Preparation 36

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.64 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1741,1694,1664 cm^{-1}

Preparation 37

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.73 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1648 cm^{-1}

Preparation 38

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (0.73 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.08 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.8–1.05 (m,24H),1.15–1.8 (m,2.7H), 2.65–3.2 (m,24H), 3.8–3.95 (m,8H),4.65–4.75 (m) and 4.9–5.5 (m) (10H),6.75–6.9 (m,4H), 7.05–7.2 (m,4H), 7.3–7.4 (m,5H)

IR (KBr): 1738,1694,1663 cm^{-1}

FAB-MS: 1227 $[M+H]^+$

Preparation 39

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OBzl (1.07 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.96 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1694,1663 cm^{-1}

Preparation 40

Boc-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (1.02 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

Preparation 41

The suspended solution of benzyl (R)-3-(4-aminophenyl)-2-hydroxypropionate (1.53 g), 1,4-dibromobutane (0.61 ml), potassium carbonate (2.07 g) and sodium iodide (0.37 g) in dimethylformamide (5 ml) were stirred at room temperature for 71 hours. To the solution was added water (50 ml) and extracted with ether (50 ml, 25 ml×2). After the ether layer was washed with saturated brine, it was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane and ethyl acetate (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-pyrrolidinophenyl) propionate (1.35 g).

NMR ($CDCl_3$,δ) 1.95–2.05 (m,4H),2.61 (d,1H),2.90 (dd, 1H),3.03 (dd,1H), 3.2–3.3 (m,4H),4.43 (ddd,1H),5.18 (s,2H),6.45 (d,2H),6.99 (d,2H),7.3–7.4 (m,5H)

IR (neat): 1732 cm^{-1}

Preparation 42

H-D-p-PyrPhLac-OBzl (1.34 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-OBzl (1.79 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ) 0.92 (d,6H),1.4–1.65 (m,12H),1.95–2.1 (m,4H),2.47 (s) and 2.52 (s) (3H),3.0–3.15 (m,2H),3.2–3.35 (m,4H),4.7–4.8 (m) and 5.0–5.25 (m) (4H),6.46 (d,2H),7.02 (d,2H), 7.1–7.2 (m,5H)

IR (KBr): 1750,1740,1692,1672 cm^{-1}

Preparation 43

Boc-MeLeu-D-p-PyrPhLac-OBzl (1.78 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-OH (1.44 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695 cm^{-1}

Preparation 44

Boc-MeLeu-D-p-PyrPhLac-OH (1.44 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (1.53 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.8–0.95 (m,12H),1.4–1.7 (m,18H), 1.95–2.05 (m,4H), 2.7–3.05 (m,8H),3.2–3.3 (m,4H), 5.65–5.75 (m) and 5.9–6.5 (m) (6H), 6.47 (d,2H),7.06 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1741,1695,1662 cm^{-1}

Preparation 45

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.65 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 46

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.77 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1743,1646 cm^{-1}

Preparation 47

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.76 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.82 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ) 0.75–1.05 (m,24H),1.1–1.75 (m,2.7H), 1.9–2.1 (m,8H), 2.65–3.1 (m,28H),3.1–3.3 (m,8H),4.6–4.8 (m) and 4.9–5.5 (m) (10H), 6.35–6.55 (m,4H),7.0–7.2 (m,4H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1664 cm^{-1}

FAB-MS: 1295 $[M+H]^+$

Preparation 48

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OBzl (0.80 g) was used instead of

Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.74 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 49

Boc-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.74 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1647 cm^{-1}

Preparation 50

1,4-dibromobutane (0.56 ml) was used instead of 1,5-dibromopentane. Except above matter, benzyl (R)-2-hydroxy-3-(4-piperidinophenyl) propionate (1.05 g). was obtained according to a similar manner to that of Preparation 41.

NMR ($CDCl_3$,δ): 1.50–1.80 (m,6H),2.65 (d,1H),2.90 (dd, 1H),3.05 (dd,1H), 3.05–3.2 (m,4H),4.44 (ddd,1H),5.17 (s,2H),6.82 (d,2H),7.01 (d,2H),7.3–7.4 (m,5H)

IR (neat): **1720**cm^{-1}

Preparation 51

H-D-p-PipPhLac-OBzl (0.79 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.71 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.90 (d,6H),1.4–1.8 (m,18H),2.62 (s) and 2.66 (s) (3H),3.0–3.15 (m,6H),4.65–4.75 (m) and 4.95–5.25 (m) (4H),6.82 (d,2H), 7.03 (d,2H),7.2–7.35 (m,5H)

IR (KBr): 1741,1695 cm^{-1}

Preparation 52

Boc-MeLeu-D-p-PipPhLac-OBzl (1.68 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-OH (1.38 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1694 cm^{-1}

Preparation 53

Boc-MeLeu-D-p-PipPhLac-OH (1.38 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (2.01 g) was obtained according to a similar manner to that of Preparation 26

NMR ($CDCl_3$,δ): 0.8–0.95 (m,12H),1.3–1.75 (m,24H), 2.7–3.15 (m,12H), 4.65–4.75 (m) and 4.9–6.4 (m,6H),6.84 (d,2H),7.09 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1695,1664 cm^{-1}

Preparation 54

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (0.99 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (0.84 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1695,1665 cm^{-1}

Preparation 55

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (0.98 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1649 cm^{-1}

Preparation 56

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (0.84 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 2HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.06 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.18 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.0 (m,24H),1.05–1.8 (m,39H), 2.65–3.2 (m,24H), 4.65–4.75 (m) and 4.9–5.5 (m) (10H), 6.8–6.9 (m,4H),7.0–7.15 (m,4H),7.3–7.4 (m,5H)

IR (KBr): 1738,1694,1663 cm^{-1}

FAB-MS: 1323 $[M+H]^+$

Preparation 57

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OBzl (1.17 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.11 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1739,1693,1662 cm^{-1}

Preparation 58

Boc-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.10 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter 3HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.24 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1742,1652 cm^{-1}

Preparation 59

Under nitrogen atmosphere, to a suspended solution of anhydrous tetrahydrofuran (1 ml) and metal magnesium (0.3 g) was added dropwise a solution of 4-(2-methoxyethoxy) bromobenzene (2.9 g) in anhydrous tetrahydrofuran (15 ml) at room temperature. After the dropping, the solution was heated under reflux at 100° C. for 15 minutes, and then the residue was cooled down to −10° C., added to cuprous bromide.dimethylsulfide complex (1.29 g), and stirred for 30 minutes at −5° C.~3° C. Further, it was cooled down to −60° C., and the solution (5 ml) of benzyl (R)-2,3-epoxypropionate (0.74 g) in anhydrous tetrahydrofuran was added dropwise for 30 minutes and stirred for 1 and ½ hour successively. To the solution were added saturated aqueous ammonium chloride (10 ml), and water (50 ml), and was extracted with ethyl acetate (100 ml×2). After washing the ethyl acetate layer with saturated brine, the solution was dried over sodium sulfate and evaporated in vacuo. The solvent was evaporated in vacuo, the resultant crude product was purified by silica get chromatography, and eluted with mixture of ethyl acetate and hexane (1:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-4-(2-methoxyethoxy) phenyl lactic acid (1.09 g).

NMR ($CDCl_3$,δ): 2.92 (dd,1H),3.06 (dd,1H),3.47 (s,3H), 3.74 (t,2H),4.08 (t,2H),4.45 (dd,1H),5.17 (s,2H),6.8 (d,2H), 7.0 (d,2H),7.29–7.48 (m,5H)

Preparation 60

H-D-p-MEPhLac-OBzl (0.92 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.15 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.90 (d,6H),1.4–1.65 (m,12H),2.6–2.7 (m,3H),3.01–3.12 (m,2H),3.45 (s,3H),3.67–3.78 (m,2H), 4.02–4.12 (m,2H),4.62–5.22 (m,4H),6.77–6.86 (m,2H), 7.02–7.12 (m,2H),7.22–7.4 (m,5H)

FAB-MS: 458 $[M-Boc+H]^+$

Preparation 61

Boc-MeLeu-D-p-MEPhLac-OBzl (1.5 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except

above matter Boc-MeLeu-D-p-MEPhLac-OH (1.29 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.03 (m,6H),1.38–1.8 (m,12H), 2.7–2.9 (m,3H), 3.0–3.3 (m,2H),3.45 (s,3H),3.65–3.78 (m,2H),4.05–4.17 (m,2H),4.4–4.51 (m) and 4.63–4.77 (m) (1H),5.2–5.38 (m,1H),6.85 (d,2H),7.13 (d,2H)

Preparation 62

Boc-MeLeu-D-p-MEPhLac-OH (1.29 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.87 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–0.95 (m,12H),1.4–1.7 (m,18H), 2.79–2.97 (m,6H), 3.01–3.09 (m,2H),3.45 (s,3H),3.64–3.79 (m,2H),4.02–4.17 (m,2H), 4.6–4.8 (m) and 4.9–5.43 (m) (6H),6.85 (d,2H),7.07–7.19 (m,2H),7.3–7.42 (m,5H)

FAB-MS: 657 $[M-Boc+H]^+$

Preparation 63

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.85 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-p-MEPhLac-MeLeu-D-Lac-OH (0.67 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.99 (m,12H),1.4–1.7 (m,18H), 2.76–2.95 (m,6H), 3.0–3.19 (m,2H),3.45 (s,3H),3.74—3.8 (m,2H),4.04–4.18 (m,2H),4.65–4.9 (m) and 5.12–5.39 (m) (4H),6.83 (d,2H),7.15 (d,2H)

Preparation 64

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.86g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter HCl.H-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.86 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.79–1.03 (m,12H),1.21–2.18 (m,9H), 2.56–2.72 (m,3H), 2.83–2.99 (m,3H),2.99–3.12 (m,2H), 3.45 (s,3H),3.63–3.8 (m,3H),4.03–4.17 (m,2H),5.03–5.58 (m,5H),6.86 (d,2H),7.07–7.43 (m,7H)

Preparation 65

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (0.66 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, HCl.H-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (0.84 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.24 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.0 (m,24H),1.15–1.79 (m,2.7H), 2.7–3.17 (m,16H), 3.45 (s,6H),3.66–3.78 (m,4H),4.02–4.14 (m,4H),4.6–4.78 (m) and 4.9–5.5 (m) (10H),6.78–6.95 (m,4H),7.03–7.18 (m,4H),7.3–7.42 (m,5H)

FAB-MS: 1205 $[M-Boc+H]^+$

Preparation 66

Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OBzl (1.22 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (1.03 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.77–1.02 (m,24H),1.18–1.8 (m,2.7H), 2.7–3.09 (m,16H), 3.45 (s,6H),3.65–3.8 (m,4H),3.98–4.17 (m,4H),4.58–5.77 (m,5H), 6.84 (d,4H),7.14 (d,4H)

Preparation 67

Under nitrogen atmosphere, at −15° C., to dichloromethane solution of (R)-isopropylidene glycerol (2 g) and triethylamine (5.05 ml) was added dropwise dichloromethane solution of trifluoromethanesulfonic anhydride (3.05 ml). After stirring for half an hour successively, dichloromethane was added and the mixture was washed with water, saturated aqueous sodium bicarbonate, saturated brine and dried over anhydrous sodium sulfate and filtrated with silica gel. The solvent was evaporated in vacuo and azeotroped by toluene to gain the crude product of triflate. To tetrahydrofuran solution of magnesium (0.61 g) was added dropwise tetrahydrofuran solution of 2-bromoanisole (2.82 ml), and for half an hour it was heated under reflux. Under ice-cooling, the copper bromide dimethylsulfide complex (0.99 g) was then added. Further tetrahydrofuran solution of the above crude product of triflate was added dropwise and stirred for 2 hours successively, aqueous ammonium chloride was added, and was extracted with ethyl acetate. The extract was dried magnesium over sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of ethyl acetate and hexane (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.25 g).

NMR ($CDCl_3$,δ): 1.35 (s,3H),1.44 (s,3H),2.81 (dd,1H), 3.02 (dd,1H),3.66 (dd,1H),3.81 (s,3H),3.88 (dd,1H),4.37 (dt, 1H),6.79–6.93 (m,2H),7.13–7.25 (m,2H)

Preparation 68

(R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.2 g) was dissolved in ethanol (20 ml) and to 6N-aqueous hydrochloric acid solution was added and stirred for 2 hours at room temperature. After evaporating ethanol in vacuo, water was added and extracted with ethyl acetate. After washing with aqueous saturated sodium bicarbonate solution, it was dried over sodium sulfate and evaporated in vacuo to give (R)-3-(2- methoxyphenyl)propane-1,2-diol (1.62 g).

NMR ($CDCl_3$,δ): 2.75–2.93 (m,2H),3.40–4.00 (m,3H), 3.85 (s,3H),6.82–6.97 (m,2H),7.12–7.28 (m,2H)

Preparation 69

Under ice-cooling, to a solution of (R)-3-(2-methoxyphenyl)propane-1,2-diol (1.62 g) and imidazole (0.92 g) in dimethylformamide was added t-butyldimethylsilyl chloride (1.36 g), and stirred for 15minutes successively. The reaction solution was poured into water, extracted with ethyl acetate, and dried over sodium sulfate. After the solvent was evaporated in vacuo, the gained crude product was purified by silica gel column chromatography, and it was eluted with a mixed solvent of hexane and ethyl acetate (7:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol (2.22 g).

NMR ($CDCl_3$,δ): 0.063 (s,6H),0.91 (s,9H),2.59 (d,1H), 2.78–2.84 (m,2H), 3.45–3.68 (m,2H),3.88 (s,3H),3.89–3.97 (m,1H),6.83–6.94 (m,2H),7.16–7.26 (m,2)

Preparation 70

Under ice-cooling, to a dichloromethane solution of (R)1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol (2.2 g) were added diisopropylethylamine (2.59 ml) and methoxymethylchloride (0.85 ml) and stirred at room temperature for 18 hours. After evaporating dichloromethane in vacuo, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the resultant crude product was purified by silica gel column chromatography, and it was eluted with a mixed solvent of hexane and ethyl acetate (6:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl)propane (2.22 g).

NMR ($CDCl_3$,δ): 0.04 (s,6H),0.89 (s,9H),2.68 (dd,1H), 2.91 (dd,1H),3.15 (s,3H),3.63 (d,2H),3.79 (s,3H),3.82–3.99 (m,1H),4.52 (d,1H),4.67 (d,1H), 6.80–6.91 (m,2H), 7.11–7.26 (m,2H)

Preparation 71

Under ice-cooling, to a tetrahydrofuran solution of (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl) propane (2.2 g) was added a solution of n tetrabutylammonium fluoride (1 mol/l, 6.46 ml) in tetrahydrofuran and stirred for 2 hours successively. After tetrahydrofuran was evaporated in vacuo, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo, the gained crude product was purified by silica gel column chromatography, and eluted with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol (1.51 g).

NMR ($CDCl_3$,δ): 2.85 (d,2H),3.36 (s,3H),3.41–3.70 (m,2H),3.83 (s,3H), 3.82–3.98 (m,1H),4.62 (d,1H),4.68 (d,1H),6.83–6.92 (m,2H),7.12–7.26 (m,2H)

Preparation 72

To dimethylformamide solution (17.5 ml) of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol (1.5 g) was added pyridinium dichromate (8.73 g) and stirred for 15 hours at room temperature. To the reaction solution was added silica gel and ethyl acetate. The mixture was filtered through silica gel. The solvent was evaporated in vacuo, ethyl acetate-benzene (1:1) was added, washed with water and dried over magnesium sulfate. After the solvent was evaporated in vacuo, tetrahydrofuran (6 ml), 6N-aqueous hydrochloric acid (6 ml) was added and stirred for 2 hours at 50° C. After tetrahydrofuran was evaporated in vacuo, water was added, extracted with ethyl acetate, washed with water, and dried over magnesium sulfate. After the solvent was evaporated in vacuo, dimethylformamide, potassium carbonate (0.7 g) was added and under ice-cooling, benzyl bromide was added dropwise. After the mixture was stirred for 1 and ½ hour, water was added, extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane and ethyl acetate (3:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(2-methoxyphenyl)propionate (1.02 g).

NMR ($CDCl_3$,δ): 2.92 (d,1H),3.03 (dd,1H),3.18 (dd,1H), 3.83 (s,3H),4.46–4.58 (m,1H),5.11 (d,1H),5.19 (d,1H), 6.83–6.91 (m,2H),7.18–7.38 (m,7H)

El-MS:286 $[M]^+$

Preparation 73

H-D-o-MeOPhLac-OBzl (1 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-OBzl (1.73 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.88 (d,6H),1.18–1.65 (m,12H), 2.58–2.78 (m,3H),2.98–3.38 (m,2H),3.79 (s,3H),4.66–5.00 (m,1H),5.08–5.18 (m,2H),5.20–5.40 (m,1H),6.76–6.89 (m,2H),7.07–7.40 (m,7H)

Preparation 74

Boc-MeLeu-D-o-MeOPhLac-OBzl (1.7 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-OH (1.54 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.95 (m,6H),1.20–1.62 (m,12H), 2.69–2.74 (m,3H), 3.02 (dd,1H),3.31–3.43 (m,1H),3.82 (s,3H),4.51–4.72 (m,1H),5.25–5.43 (m,1H),6.80–6.92 (m,2H),7.11–7.26 (m,2H)

Preparation 75

Boc-MeLeu-D-o-MeOPhLac-OH (1.5 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (2.09 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.99 (m,12H),1.20–1.80 (m,18H), 2.70–3.34 (m, 8H),3.84 (s) and 3.79 (s) (3H),4.59–5.58 (m,6H),6.81–6.92 (m,2H),7.13–7.35

Preparation 76

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (0.98 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.01 (m,12H),1.10–1.78 (m,18H), 2.69–3.21 (m,8H), 3.86 (s,3H),4.62–5.92 (m,4H),6.81–6.92 (m,2H),7.12–7.26 (m,2H)

Preparation 77

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-o MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.68–1.01 (m,12H),1.10–1.98 (m,9H), 2.56–3.40 (m,8H), 3.67–3.82 (m,1H),3.84 (s,3H),4.95–5.72 (m,5H),6.81–6.93 (m,2H), 7.15–7.36 (m,7H)

Preparation 78

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (0.98 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (0.94 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1.26 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.79–1.00 (m,24H),1.19–1.82 (m,2.7H),2.72–3.19 (m,16H), 3.79–3.92 (m,6H),4.61–5.62 (m,10H),6.77–6.93 (m,4H),7.17–7.38 (m,9H)

Preparation 79

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OBzl (1.25g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (1.24 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.00 (m,24H),1.15–1.82 (m,2H), 2.62–3.22 (m,16H), 3.85 (s,6H),4.42–5.90 (m,8H), 6.80–6.92 (m,4H),0.15–7.26 (m,4H)

Preparation 80

3-bromoanisole (2.82 ml) was used instead of 2-bromoanisole. Except above matter, (R)-4-(3-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (2.25 g) was obtained according to a similar manner to that of Preparation 67.

NMR ($CDCl_3$,δ): 1.36 (s,3H),1.44 (s,3H),2.73 (dd,1H), 3.00 (dd,1H),3.61 (dd,1H),3.79 (s,3H),3.97 (dd,1H),4.32 (dt,1H),6.76–6.82 (m,3H),7.17–7.23 (m,1H)

Preparation 81

(R)-4-(3-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane (1.3 g) was used instead of (R)-4-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxolane. Except above matter, (R)-3-(3-methoxyphenyl)propane-1,2-diol (1 g) was obtained according to a similar manner to that of Preparation 68.

NMR ($CDCl_3$,δ): 1.93 (t,1H),2.06 (d,1H),2.67–2.82 (m,2H),3.47–3.79 (m,2H),3.81 (s,3H),3.90–4.02 (m,1H), 6.77–6.84 (m,3H),7.20–7.28 (m,1H)

Preparation 82

(R)-3-(3-methoxyphenyl)propane-1,2-diol (0.99 g) was used instead of (R)-3-(2-methoxyphenyl)propane-1,2-diol. Except above matter, (12)-1-t-butyldimethylsiloxy-3-(3-methoxyphenyl)-2-propanol (1.4 g) was obtained according to a similar manner to that of Preparation 69.

NMR ($CDCl_3$,δ): 0.065 (s,6H),0.91 (s,9H),2.40 (d,1H), 2.75 (d,2H),3.45 (dd,1H),3.61 (dd,1H),3.79 (s,3H), 3.85–4.00 (m,1H),6.75–6.83 (m,3H),7.17–7.26 (m,1H)

Preparation 83

(R)-1-t-butyldimethylsiloxy-3-(3-methoxyphenyl)-2-propanol (1.4 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol. Except above matter (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy 3-(3-methoxyphenyl)propane (1.5 g) was obtained according to a similar manner to that of Preparation 70.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.91 (s,9H),2.71 (dd,1H), 2.89 (dd,1H),3.16 (s,3H),3.53–3.68 (m,2H),3.80 (s,3H), 3.79–3.90 (m,1H),4.51 (d,1H),4.68 (d,1H),6.72–6.85 (m,3H),7.11–7.20 (m,1H)

Preparation 84

(R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(3-methoxyphenyl)propane (1.5 g) was used instead of (R)-1t-butyldimethylsiloxy-2-methoxymethoxy-3-(2-methoxyphenyl)propane. Except above matter, (R)-2-methoxymethoxy-3-(3-methoxyphenyl)-1-propanol (0.93 g) was obtained according to a similar manner to that of Preparation 71.

NMR ($CDCl_3$,δ): 2.69–2.92 (m,2H),3.35 (s,3H), 3.45–3.68 (m,2H),3.79 (s,3H),3.70–3.86 (m,1H),4.57 (d,1H),4.68 (d,1H),6.73–6.83 (m,3H),7.16–7.26 (m,1H)

Preparation 85

(R)-2-methoxymethoxy-3-(3-methoxyphenyl)-1-propanol (0.93 g) was used instead of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol. Except above matter, benzyl (R)-2-hydroxy-3-(3-methoxyphenyl)propionate (0.61 g) was obtained according to a similar manner to that of Preparation 72.

NMR ($CDCl_3$,δ): 2.72 (d,1H),2.95 (dd,1H),3.10 (dd,1H), 3.77 (s,3H),4.41–4.55 (m,1H),5.18 (s,2H),6.71–6.80 (m,3H),7.13–7.39 (m,6H)

Preparation 86

H-D-m-MeOPhLac-OBzl (0.6 g) was used instead of HD-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.26–1.57 (m,12H), 2.62–2–2.75 (m,3H),3.02–3.22 (m,2H),3.76 (s,3H), 4.62–5.30 (m,4H),6.73–6.79 (m,3H),7.14–7.34 (m,6H)

Preparation 87

Boc-MeLeu-D-m-MeOPhLac-OBzl (lg) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-OH (0.93 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–0.98 (m,6H),1.30–1.80 (m,12H), 2.64–2.80 (m,3H), 3.03–3.32 (m,2H),3.79 (s,3H),4.42–5.40 (m,2H),6.76–6.84 (m,3H), 7.16–7.26 (m,1H)

Preparation 88

Boc-MeLeu-D-m-MeOPhLac-OH (0.93 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (1.28 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.99 (m,12H),1.20–1.75 (m,18H), 2.75–2.92 (m,6H), 3.00–3.20 (m,2H),3.78 (s,3H),4.62–5.50 (m,6H),6.76–6.84 (m,3H), 7.17–7.39 (m,6H)

Preparation 89

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.64 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.6 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–0.98 (m,12H),1.10–1.75 (m,18H), 2.73–3.22 (m,8m), 3.78 (s,3H),4.60–5.85 (m,4H),6.75–6.85 (m,3H),7.18–7.25 (m,1H)

Preparation 90

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.61 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.6 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.62–1.00 (m,12H),1.10–1.98 (m,9H), 2.56–3.10 (m,8H), 3.70–3.82 (m,1H),3.79 (s,3H),5.02–5.59 (m,5H),6.75–6.90 (m,3H), 7.15–7.40 (m,6H)

Preparation 91

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.6 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH and HCl.H-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.6 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.82 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.70–1.02 (m,24H),1.20–1.79 (m,2.7H),2.70–3.19 (m,16), 3.78 (s,6H),5.01–5.60 (m,10H), 6.70–6.92 (m,6H),7.18–7.34 (m,7H)

Preparation 92

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OBzl (0.82 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.79 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.75–1.00 (m,24H),1.10–1.80 (m,2.7H),2.60–3.19 (m,16H), 3.78 (s,6H),4.58–5.78 (m,8H),6.71–6.90 (m,6H),7.12–7.35 (m,2H)

Preparation 93

1-bromo-3,4-dimethoxybenzene (1.83 g) was used instead of 4-(2-methoxyethoxy) bromobenzene. Except above matter, benzyl (R)-2-hydroxy-3-(3,4-dimethoxyphenyl)propionate (0.23 g) was obtained according to a similar manner to that of

Preparation 59.

NMR ($CDCl_3$,δ): 2.71 (d,1H),2.93 (dd,1H),3.08 (dd,1H), 3.79 (s,3H),3.85 (s,3H),4.42–4.55 (m,1H),5.19 (s,2H), 6.65–6.76 (m,3H),7.26–7.40 (m,5H)

Preparation 94

H-D-3,4-DMOPhLac-OBzl (0.23 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-OBzl (0.34 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.39–1.62 (m,12H), 2.62–2.73 (m,3H),3.0–3.19 (m,2H),3.82 (s,3H),3.85 (s,3H), 4.62–5.32 (m,4H),6.65–6.80 (m,3H), 7.20–7.40 (m,5H)

Preparation 95

Boc-MeLeu-D-3,4-DMOPhLac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-OH (0.3 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.85–0.96 (m,6H),1.42 (s,9H), 1.22–1.69 (m,3H),2.73–2.82 (m,3H),2.95–3.22 (m,2H),3.85 (s,3H),3.87 (s,3H),4.38–4.70 (m,1H), 5.21–5.39 (m,1H), 6.72–6.83 (m,3H)

Preparation 96

Boc-MeLeu-D-3,4-DMOPhLac-OH (0.3 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.41 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.82–0.98 (m,12H),1.35–1.69 (m,18H), 2.77–3.15 (m,8H), 3.85 (s,3H),3.87 (s,3H),4.62–5.48 (m,6H),6.72–6.80 (m,3H),7.26–7.39 (m,5H)

Preparation 97

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.2 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.00 (m,12H),1.24–1.80 (m,18H), 2.74–3.16 (m,8H), 3.85 (s,3H),3.87 (s,3H),4.59–5.78 (m,4H),6.77 (s,3H)

Preparation 98

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.18 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.78–0.98 (m,12H),1.20–2.00 (m,9H), 2.62–3.15 (m,8H), 3.69–3.82 (m,1H),3.85 (s,3H),3.87 (s,3H),5.02–5.60 (m,5H),6.74–6.82 (m,3H),7.22–7.38 (m,5H)

Preparation 99

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.2 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.18 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.27 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.70–1.00 (m,24H),1.20–1.79 (m,2.7H),2.72–3.18 (m,16H), 3.84 (s,6H),3.86 (s,6H), 4.62–5.48 (m,10H),6.72–6.83 (m,6H),7.21– 7.40 (m,5H)

Preparation 100

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.26 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-OH (0.26 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.76–1.02 (m,24H),1.32–1.75 (m,2.7H),2.72–3.20 (m,16H), 3.85 (s,6H),3.87 (s,6H), 4.60–5.70 (m,8H),6.72–6.80 (m,6H)

Preparation 101

1-bromo-2,4-dimethoxybenzene (2.93 g) was used instead of 4-(2-methoxyethoxy)bromobenzene. Except above matter, benzyl (R)-2-hydroxy-3-(2,4-dimethoxyphenyl)propionate (1.28 g) was obtained according to a similar manner to that of

Preparation 59.

NMR ($CDCl_3$,δ): 2.87 (d,1H),2.96 (dd,1H),3.10 (dd,1H), 3.76 (s,3H),3.78 (s,3H),4.43–4.53 (m,1H),5.12 (d,1H),5.19 (d,1H),6.36–6.43 (m,2H),6.99 (d,1H),7.21–7.40 (m,5H)

Preparation 102

H-D-2,4-DMOPhLac-OBzl (1.27 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-OBzl (2.16 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.36–1.60 (m,12H), 2.61–2.70 (m,3H),2.92–3.29 (m,2H),3.76 (s,3H),3.77 (s,3H),4.60–5.35 (m,4H),6.31–16.40 (m, 2H),6.97 (d,1H), 7.19–7.40 (m,5H)

Preparation 103

Boc-MeLeu-D-2,4-DMOPhLac-OBzl (2.15 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-OH (1.61 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–0.93 (m,6H),1.38–1.62 (m,12H), 2.73 (brs,3H), 2.91–3.39 (m,2H),3.78 (s,6H),4.58–4.70 (m,1H),5.20–5.39 (m,1H),6.37–6.44 (m,2H),7.03 (d,1H)

Preparation 104

Boc-MeLeu-D-2,4-DMOPhLac-OH (1.6 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (2.2 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.05 (m,12H),1.32–1.65 (m,18H), 2.75–3.15 (m,8H), 3.78 (s,3H),3.81 (s,3H),4.60–5.60 (m,6H),6.30–6.46 (m,2H),7.00–7.09 (m,1H),7.25–7.40 (m,5H)

Preparation 105

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.15–1.78 (m,18H), 2.70–3.12 (m,8H), 3.78 (s,3H),3.83 (s,3H),4.60–5.87 (m,4H),6.30–6.42 (m,2H),7.04 (d,1H)

Preparation 106

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.98 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.69–1.02 (m,12H),1.20–2.00 (m,9H), 2.58–3.20 (m,8H), 3.70–3.80 (m,1H),3.78 (s,3H),3.81 (s,3H),5.00–5.71 (m,5H),6.37–6.46 (m,2H),7.07 (d,1H), 7.20–7.42 (m,5H)

Preparation 107

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (0.98 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.48 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.82–1.00 (m,24H),1.15–1.80 (m,2.7H),2.75–3.21 (m,16H), 3.72–3.84 (m,12H),4.60–5.60 (m,10H),6.31–6.49 (m,4H),7.00–7.17 (m,2H),7.21–7.40 (m,5H)

Preparation 108

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OBzl (1.45 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-OH (1.49 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δd): 0.80–1.02 (m,24H),1.20–1.90 (m,2.7H),2.71–3.22 (m,16H), 3.81 (s) and 3.78 (s) (12H), 4.60–5.80 (m,8H),6.33–6.46 (m,4H), 7.01–7.15 (m,2H)

Preparation 109

1-bromo-3,4-methylenedioxybenzene (2.05 ml) was used instead of 2-bromoanisole. Except above matter, (R)-4-(3,4-methylenedioxybenzyl)-2,2-dimethyl-1,3-dioxolane (1.64 g) was obtained according to a similar manner to that of Preparation 67.

NMR ($CDCl_3$,δ): 1.35 (s,3H),1.43 (s,3H),2.69 (dd,1H), 2.91 (dd,1H),3.62 (dd,1H),3.97 (dd,1H),4.27 (dt,1H),5.93 (s,2H),6.58–6.78 (m,3H)

Preparation 110

(R)-2,2-dimethyl-5-(3,4-methylenedioxybenzyl)-1,3-dioxolane (1.63 g) was used instead of (R)-2,2-dimethyl-5-(2-methoxybenzyl)-1,3-dioxolane. Except above matter, (R)-3-(3,4-methylenedioxyphenyl)propane-1,2-diol (1.37 g) was obtained according to a similar manner to that of Preparation 68.

NMR ($CDCl_3$,δ): 2.63 (dd,1H),2.72 (dd,1H),3.48 (dd, 1H),3.67 (dd,1H), 3.80–3.96 (m,1H),5.92 (s,2H),6.58–6.78 (m,3H)

Preparation 111

(R)-3-(3,4-methylenedioxyphenyl)-propane-1,2-diol (1.25 g) was used instead of (R)-3-(2-methoxyphenyl)propane-1,2-diol. Except above matter, (R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-propanol (1.77 g) was obtained according to a similar manner to that of Preparation 69.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.91 (s,9H),2.69 (d,2H), 3.46 (dd,1H),3.61 (dd,1H),3.79–3.85 (m,1H),5.93 (s,2H), 6.63–6.77 (m,3H)

Preparation 112

(R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-propanol (1.77 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-propanol. Except above matter, (R)-1-t-butyldimethylsiloxy-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)propane (1.79 g) was obtained according to a similar manner to that of Preparation 70.

NMR ($CDCl_3$,δ): 0.07 (s,6H),0.90 (s,9H),2.65 (dd,1H), 2.83 (dd,1H),3.20 (s,3H),3.52–3.62 (m,2H),3.71–3.83 (m,1H),4.52 (d,1H),4.68 (d,1H),5.92 (s,2H),6.64–6.75 (m,3H)

Preparation 113

(R)-1-t-butyldimethylsiloxy-3-(3,4-methylenedioxyphenyl)-2-methoxymethoxypropane (1.77 g) was used instead of (R)-1-t-butyldimethylsiloxy-3-(2-methoxyphenyl)-2-methoxymethoxypropane. Except above matter, (R)-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)-1-propanol (1.17 g) was obtained according to a similar manner to that of Preparation 71.

NMR ($CDCl_3$,δ): 2.69 (dd,1H),2.79 (dd,1H),3.37 (s,3H), 3.49 (dd,1H),3.63 (dd,1H),3.71–3.82 (m,1H),4.58 (d,1H), 4.68 (d,1H),5.93 (s,2H),6.62–6.78 (m,3H)

Preparation 114

(R)-2-methoxymethoxy-3-(3,4-methylenedioxyphenyl)-1-propanol (0.92 g) was used instead of (R)-2-methoxymethoxy-3-(2-methoxyphenyl)-1-propanol. Except above matter, benzyl (R)-2-hydroxy-3-(3,4-methylenedioxyphenyl)propionate (0.33 g) was obtained according to a similar manner to that of Preparation 72.

NMR ($CDCl_3$,δ): 2.72 (d,1H),2.88 (dd,1H),3.04 (dd,1H), 4.38–4.55 (m,1H), 5.19 (s,2H),5.92 (s,2H),6.53–6.70 (m,3H),7.25–7.40 (m,5H)

Preparation 115

H-D-3,4-MODPhLac-OBzl (0.5 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-OBzl (0.74 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.91 (d,6H),1.38–1.70 (m,12H), 2.62–2.83 (m,3H),2.98–3.20 (m,2H),4.55–5.26 (m,4H),5.92 (s,2H),6.52–6.75 (m,3H),7.21–7.40 (m,5H)

Preparation 116

Boc-MeLeu-D-3,4-MODPhLac-OBzl (0.73 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-OH (0.63 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,6H),1.20–1.80 (m,12H), 2.63–2.93 (m,3H), 2.95–3.25 (m,2H),4.43–4.90 (m,1H), 5.09–5.36 (m,1H),5.93 (s,2H),6.60–6.82 (m,3H)

Preparation 117

Boc-MeLeu-D-3,4-MODPhLac-OH (0.63 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.85 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.20–1.82 (m,18H), 2.69–3.06 (m,8H), 4.60–5.60 (m,6H),5.88–5.97 (m,2H), 6.68–6.80 (m,3H),7.26–7.40 (m,5H)

Preparation 118

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.42 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-MOD-PhLac-MeLeu-D-Lac-OH (0.393)was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.80–1.00 (m,12H),1.20–1.80 (m,18H), 2.65–3.20 (m,8H), 4.60–5.80 (m,4H),5.93 (s,2H),6.62–6.78 (m,3H)

Preparation 119

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.43 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBz. Except above matter, HCl.H-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.4 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ):0.78–1.05 (m,12H),1.20–2.40 (m,9H), 2.60–3.25 (m,8H), 3.60–3.90 (m,1H),5.02–5.58 (m,5H), 5.85–5.98 (m,2H),6.65–6.92 (m,3H),7.20–7.42 (m,5H)

Preparation 120

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.4 g) was used instead of HCl.H-MeLeu-D-Lac-OBz. Except above matter. Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.05 (m,24H),1.15–1.90 (m,2.7H),2.62–3.15 (m,16H), 4.60–5.60 (m,10H),5.85–5.96 (m,4H),6.60–6.80 (m,6H),7.26–7.40 (m,5H)

Preparation 121

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OBzl (0.59 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.59 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.75–1.00 (m,24H),1.15–1.82 (m,2.7H),2.62–3.20 (m,16H), 4.56–5.63 (m,8H),5.92 (s,4H),6.60–6.80 (m,6H)

Preparation 122

To a solution of 3-nitro-L-tyrosine (4.52 g) in dioxane (40 ml) was added 1N sodium hydroxide solution (40 ml), and further di-t-butyldicarbonate (4.8 g) was added and stirred for 1 hour at room temperature. To the reaction was added water (200 ml) and extracted with ethyl acetate (100 ml×3).

After the ethyl acetate layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give N-(t-butoxycarbonyl)-3-nitro-L-tyrosine (6.50 g).

NMR ($CDCl_3$,δ):1.42 (s,9H),2.9–3.3 (m,3H),4.6–4.65 (m) and 5.05 –5.15 (m) (1H),7.09 (d,1H),7.44 (dd,1H),7.93 (d,1H),10.4–10.6 (m,1H)

IR (KBr): 1713,1683 cm^{-1}

Preparation 123

To a solution of N-(t-butoxycarbonyl)-3-nitro-L-tyrosine (6.49 g) in dimethylformamide (50 ml) was added potassium carbonate (11.05 g). Further methyl iodide (3.7 ml) was added and stirred for 15 hours at room temperature. To the reaction solution was added water (500 ml) and extracted with ethyl acetate (100 ml×3). After ethyl acetate layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give methyl N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.76 g).

NMR ($CDCl_3$,δ): 1.42 (s,9H),3.00 (dd,1H)),3.17 (dd,1H), 3.75 (s,3H),3.95 (s,3H),4.5–4.65 (m) and 5.0–5.1 (m) (1H), 7.02 (d,1H),7.33 (dd,1H),7.62 (d,1H)

IR (KBr): 1742,1710,1695 cm^{-1}

Preparation 124

To a ethanol solution of methyl N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.74 g) was added 1N sodium hydroxide solution (25 ml) and was stirred for 2 hours at room temperature. The solvent was evaporated and water (70 ml) and 1N hydrochloric acid solution (27.5 ml) was added, extracted with ethyl acetate (50 ml×3). After ethyl acetate layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. To the residue was added hexane and ether and it was crystallized to give N-(t-butoxycarbonyl) -O-methyl-3-nitro-L-tyrosine (6.61 g).

NMR ($CDCl_3$,δ): 1.42 (s,9H),2.9–3.3 (m,2H),3.95 (s,3H), 4.5–4.65 (m) and 5.0–5.1 (m) (1H),7.27 (d,1H),7.39 (dd, 1H)),7.69(bs,1H)

IR (KBr): 1727,1652 cm^{-1}

Preparation 125

To N-(t-butoxycarbonyl)-O-methyl-3-nitro-L-tyrosine (6.60 g) was added 4N hydrogen chloride in ethyl acetate solution and was stirred for 1 hour at room temperature. The solvent was evaporated and further it was azeotroped by toluene to give O-methyl-3-nitro-L-tyrosine hydrochloride (4.95 g).

NMR (DMSO-d_6,δ): 3.1–3.2 (m,2H),3.92 (s,3H),4.21 (t,1H),7.35 (d,1H), 7.59 (dd,1H),7.83 (d,1H)

IR (KBr): 1729 cm^{-1}

Preparation 126

To suspension solution of O-methyl-3-nitro-L-tyrosine-.hydrochloride (4.93 g) in 6N aqueous hydrochloric acid was added under ice-cooling, sodium nitrite (1.97 g) and was stirred at the same temperature for 1 and ½ hour and further at room temperature for 3 hours. The resultant suspension solution was extracted with ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to give (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionic acid (4.46 g).

NMR ($CDCl_3$,δ): 3.21 (dd,1H),3.39 (dd,1H),3.96 (s,3H), 4.49 (dd,1H) 7.06 (d,1H),7.45 (dd,1H),7.77 (d,1H)

IR (neat): 1726 cm^{-1}

Preparation 127

To a ethanol solution of (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionic acid (4.46 g) was added p toluenesulfonic acid (0.38 g) and heated under reflux for 5 hours. After cooled it down, the solvent was evaporated in vacuo. The resultant suspension solution was extracted by ethyl acetate (50 ml×3). After the ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel column chromatography, and eluted with mixture of hexane or ethyl acetate (4:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionate (4.51 g)

NMR ($CDCl_3$,δ): 1.26 (t,3H),3.17 (dd,1H),3.36 (dd,1H)), 3.96 (s,3H),4.15 (q,2H),4.41 (dd,1H) 7.03 (d,1H),7.43 (dd, 1H),7.74 (d,1H)

IR (neat): 1735 cm^{-1}

Preparation 128

To a ethanol solution (50 ml) which contain acetic acid (2.3 ml) was added cesium carbonate (6.5 g) and stirred for a half an hour at room temperature, and the solvent was evaporated to give cesium acetate. Cesium acetate was added to dimethylformamide solution of ethyl (S)-2-chloro-3-(4-methoxy-3-nitrophenyl)propionate (4.51 g) and stirred for 4 hours. To the mixture, water (200 ml) was added and extracted with ether (100 ml×1, 50 ml×2). After ether layer was washed with saturated brine, the residue was dried over anhydrous sodium sulfate and evaporated in vacuo. The resultant crude product was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-2-acetoxy-3-(4-methoxy-3-nitrophenyl)propionate (1.58 g).

NMR ($CDCl_3$,δ): 1.26 (t,3H),2.11 (s,3H),3.05–3.25 (m,2H),3.95 (s,3H), 4.20 (q,2H),5.19 (dd,1H) 7.03 (d,1H), 7.42 (dd,1H),7.74 (d,1H)

IR (neat): 1742 cm^{-1}

Preparation 129

To a ethanol solution (50 ml) which contain 37% aqueous formalin solution (4.0 ml) of ethyl (R)-2-acetoxy-3-(4-methoxy-3-nitrophenyl)propionate (1.56 g) was added 10% palladium on carbon (0.5 g) and under atmospheric pressure hydrogenated at room temperature for 4 hours. The catalyst was filtered off and the solvent was evaporated in vacuo. The resultant crude product was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (7:3, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-2-acetoxy-3-(4-methoxy-3-dimethylaminophenyl-)propionate (1.58 g).

NMR ($CDCl_3$,δ): 1.23 (t,3H),2.09 (s,3H),2.77 (s,6H), 2.95–3.15 (m,2H), 3.87 (s,3H),4.18 (q,2H),5.15 (dd,1H) 6.75–6.9 (m,3H)

IR (neat): 1742 cm^{-1}

Preparation 130

To a solution of ethyl (R)-2-acetoxy-3-(4-methoxy-3-dimethylaminophenyl)propionate (1.56 g) in benzyl alcohol (3.7 ml) and benzene (7.4 ml) was added p-toluenesulfonic acid (0.82 g) and heated under reflux for 6 hours. After cooling, the solvent was evaporated in vacuo, and the gained crude product was purified by silica gel column chromatography. The residue was eluted with mixed solvent of hexane, ethyl acetate, and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (R)-2-hydroxy-3-(4-methoxy-3-dimethylaminophenyl)propionate (0.93 g).

NMR ($CDCl_3$,δ): 2.68 (d,1H),2.74 (s,6H),2.92 (dd,1H), 5.19 (s,2H) 6.7–6.8 (m,3H),7.3–7.4 (m,5H)

IR (KBr): 1738 cm^{-1}

Preparation 131

H-D-3MA-4MOPhLac-OBzl (0.90 g) was used instead of H-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.40 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.41 (s) and 1.47 (s) (9H), 1.4–1.6 (m,3H), 2.65 (s) and 2.68 (s) (3H),2.75 (s,6H), 3.1–3.2 (m,2H),3.85 (s,3H),4.6–4.75 (m) and 4.95–5.3 (m) (4H),6.7–6.8 (m,3H),7.2–7.4 (m,5H)

IR (KBr): 1741,1695 cm^{-1}

Preparation 132

Boc-MeLeu-D-3MA-4MOPhLac-OBzl (1.38 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBz. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-OH (1.16 g) was obtained according to a similar manner to that of Preparation 25.,

IR (KBr): 1740,1694 cm^{-1}

Preparation 133

Boc-MeLeu-D-3MA-4MOPhLac-OH (1.16 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.80 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.1 (m,12H),1.35–1.7 (m,18H), 2.65–3.1 (m,12H), 3.0–3.1 (m,2H),3.85 (s,3H),4.60–3.8 (m) and 4.9–5.5 (m) (6H), 6.7–6.85 (m,3H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1664 cm^{-1}

Preparation 134

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.90 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (0.85 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1696,1662 cm^{-1}

Preparation 135

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.90 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac MeLeu-D-Lac-OBzl. Except above matter, 2HCl.H-MeLeu-D-MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.97 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1744,1648 cm^{-1}

Preparation 136

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (0.84 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and 2HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (0.96 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.15 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.75–1.05 (m,24H),1.3–1.8 (m,2.7H), 2.6–3.2 (m,16H), 2.77 (s,12H),3.85 (s,6H),4.65–4.75 (m) and 4.9–5.5 (m) (10H),6.7–6.9 (m,6H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1663 cm^{-1}

FAB-MS: 1303 $[M+H]^+$

Preparation 137

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OBzl (1.14 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.09 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1740,1694,1663 cm^{-1}

Preparation 138

Boc-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.08 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-OH (1.19 g) was obtained according to a similar manner to that of

Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

Preparation 139

To a dichloromethane solution of ethyl D-2-hydroxy-3-(4-aminophenyl)propionate (4.2 g) were added under ice-cooling, triethylamine (7.36 ml), acetyl chloride (2.5 g) at room temperature for 2 and ½ hours. The reaction solution was poured into aqueous saturated sodium bicarbonate solution, and extracted with dichloromethane. After drying by magnesium sulfate, the solvent was evaporated in vacuo and then purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-3-(4-acetamidephenyl)-2-acetoxypropionate (3.42 g).

NMR ($CDCl_3$,δ): 1.24 (t,3H),2.08 (s,3H),2.16 (s,3H), 3.06–3.20 (m,2H), 4.17 (q,2H),5.12–5.20 (m,1H),7.17 (d,2H),7.43 (d,2H)

Preparation 140

To an anhydrous acetic acid solution of ethyl (R)-3-(4-acetamidephenyl)-2-acetoxypropionate (3.12 g) was added dropwise under ice-cooling, fuming nitric acid (3 ml)—acetic anhydride (7.5 ml), and stirred for a half an hour successively. The reaction solution was poured into aqueous saturated sodium bicarbonate solution, after the neutralization, extracted with ethyl acetate, and washed with saturated brine. After drying by magnesium sulfate, the solvent was evaporated in vacuo to give ethyl (R)-3-(4-acetamide-3-nitrophenyl)-2-acetoxypropionate (3.98 g)

NMR ($CDCl_3$,δ): 1.25 (t,3H),2.11 (s,3H),2.29 (s,3H), 3.10–3.25 (m,2H), 4.50 (q,2H),5.17–5.24 (m,1H),7.52 (dd, 1H),8.10 (d,1H),8.72 (d,1H)

Preparation 141

To a solution of ethyl (R)-3-(4-acetamide-3-nitrophenyl)-2-acetoxypropionate (3.9 g) in ethanol (120 ml) was added concentrated hydrochloric acid and heated under reflux for 75 minutes. After ethanol was evaporated in vacuo, aqueous saturated sodium bicarbonate solution was added, extracted with ethyl acetate, and washed with saturated sodium chloride. After drying by magnesium sulfate, the solvent was evaporated in vacuo to give ethyl (R)-3-(4-amino-3-nitrophenyl)-2-hydroxypropionate (2.59 g).

NMR ($CDCl_3$,δ): 1.32 (t,3H),2.89 (dd,1H),3.05 (dd,1H), 4.23 (q,2H),4.35–4.50 (m,1H),6.74 (d,1H),7.30 (dd,1H)), 7.30 (d,1H)

Preparation 142

To a solution of ethyl (R)-3-(4-amino-3-nitrophenyl)-2-hydroxypropionate (0.8 g) in methanol (8 ml) and water (5 ml) were added iron powder (1 g), acetic acid (0.8 ml) and heated under reflux for a half an hour. After the reaction solution was filtered through celite, methanol was evaporated in vacuo. After the residue was neutralized with aqueous sodium bicarbonate solution, the residue was extracted with ethyl acetate. After drying by magnesium sulfate, the solvent was evaporated in vacuo, and dissolved in acetic acid. To the mixture paraformaldehyde (0.56 g), and sodium cyanoborohydride (0.59 g) were added and stirred for 19 hours at room temperature. The reaction

solution was added to aqueous solution saturated with sodium bicarbonate, and after the residue was neutralized with aqueous sodium bicarbonate solution, extracted with ethyl acetate, and dried over sodium sulfate. The solvent was evaporated in vacuo and then purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (3:2, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain ethyl (R)-3-[3,4-bis (dimethylamino)phenyl]-2-hydroxypropionate (0.3 g).

NMR ($CDCl_3$,δ): 1.29 (t,3H),2.65 (s,6H),2.77 (s,6H), 2.75–3.16 (m,2H), 4.23 (q,2H),4.35–4.50 (m,1H),6.70–6.83 (m,2H),7.21–7.26 (m,1H)

El-MS: 281 $[M]^+$

Preparation 143

To a solution of ethyl (R)-3-[3,4-bis(dimethylamino)phenyl]-2-hydroxypropionate (0.54 g) in benzene were added benzyl alcohol (2 ml) and 13-toluenesulfonic acid (0.8 g) and heated under reflux for 5 hours. The reaction solution was added to aqueous dilute hydrochloric acid, after washing with ethyl acetate, the water layer was neutralized with aqueous saturated sodium bicarbonate, and extracted with ethyl acetate. After washing with saturated sodium chloride, dried over sodium sulfate. After the solvent was evaporated in vacuo, purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (3:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (12)-3-[3,4-bis(dimethylamino)phenyl]-2-hydroxypropionate (0.3 g).

NMR ($CDCl_3$,δ): 2.74 (s,6H),2.75 (s,6H),2.91 (dd,1H), 3.05 (dd,1H),4.40–4.55 (m,1H),5.15 (d,1H),5.22 (d,1H), 6.60–6.80 (m,3H),7.25–7.40 (m,5H)

IR (KBr): 1734 cm^{-1}

Preparation 144

H-D-3,4-DMAPhLac-OBzl (0.32 g) was used instead of H-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 24.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.32–1.60 (m,12H), 2.60–2.70 (m,3H),2.75 (s,12H),3.00–3.20 (m,2H),4.62–5.30 (m,4H),6.65–6.78 (m,3H),7.20–7.40 (m,5H)

Preparation 145

Boc-MeLeu-D-3,4-DMAPhLac-OBzl (0.59 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-OH (0.47 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.20–1.80 (m,12H), 2.60–2.85 (m,15H), 3.00–3.28 (m,2H),4.30–4.80 (m) and 5.18–5.37 (m) (2H),6.78–6.90 (m,3H)

Preparation 146

Boc-MeLeu-D-3,4-DMAPhLac-OH (0.47 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.67 g) was obtained according to a similar manner to that of

Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.00 (m,12H),1.38–1.70 (m,18H), 2.71–3.18 (m,20H), 4.60–5.57 (m,6H),6.66–6.80 (m,3H), 7.22–7.38 (m,5H)

Preparation 147

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.30 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.08 (m,12H),1.20–1.75 (m,18H), 2.62–3.23 (m,20H), 4.60–5.82 (m,4H),6.72–6.84 (m,3H)

Preparation 148

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.33 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, 3HCl.H-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.30 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.76–1.12 (m,12H),1.25–2.20 (m,9H), 2.60–4.20 (m,21H), 5.05–5.60 (m,5H),7.20–7.62 (m,7H), 8.30–8.50 (m,1H),9.42–9.70 (m,1H),10.92–11.20 (m,1H)

Preparation 149

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.30 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, 3HCl.H-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.30 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OBzl (0.35 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.78–1.00 (m,24H),1.20–1.80 (m,2.7H),2.63–3.18 (m,40H), 4.90–5.60 (m,10H),6.65–6.80 (m,6H),7.22–7.38 (m,5H)

FAB-MS: 1330 $[M+H]^+$

Preparation 150

Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMAPhLac-MeLeu-D-m-Lac-OBzl (0.34 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-OH (0.35 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.07 (m,24H),1.10–1.80 (m,27H), 2.30–3.20 (m, 40H),4.60–5.74 (m,8H),6.70–6.82 (m,6H)

Preparation 151

(S)-2-fluorophenyl alanine (3.00 g) was dissolved in 6N -aqueous hydrochloric acid (80 ml) and at 0° C. sodium nitrite (3.01 g) was added gradually. After the mixture was stirred for 4 hours successively, the temperature was increased back to room temperature. To the mixture was added sodium nitrite (1.13 g), stirred further for 2 hours, added water (200 ml), and extracted with ether (150 ml×1, 100 ml×2). The ether layer was washed with a solution (saturated brine: water=1:1, v/v) (100 ml×2), dried over calcium chloride, and the solvent was evaporated in vacuo. To the residue, benzene (20 ml), benzylalcohol (1.32 ml) and p-toluenesulfonic acid mono hydrate (0.33 g) were added and heated under reflux for an hour using Dean-stark apparatus. After cooling down to room temperature, the crude product, which was gained by evaporating the solvent, was purified by silica gel chromatography, eluting with a mixed solvent of ethyl acetate and hexane (1:19 V/V). The fractions containing the desired product were combined and evaporated in vacuo to obtain benzyl (S)-2-chloro-3-(2-fluorophenyl)propionate (2.24 g).

NMR ($CDCl_3$,δ): 3.25 (dd,1H),3.40 (dd,1H),4.57 (t,1H), 5.16 (s,2H),6.98– 7.40 (m,9H)

EI-MS: 292 $[M]^+$

Preparation 152

Benzyl (S)-2-chloro-3-(2-fluorophenyl)propionate (0.90 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-o-FPhLac-OBzl (1.30 g) was obtained according to a similar matter to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.89 (d,6H),1.38–1.63 (m,12H), 2.58–2.70 (m,3H),3.10– 3.38 (m,2H),4.6–4.78 (m) and 5.1–5.38 (m) (4H),6.97–7.42 (m,9H)

FAB-MS: 402 [M-Boc+H]$^+$

Preparation 153

Boc-MeLeu-D-o-FPhLac-OBzl (1.26 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-OH (1.07 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.02 (m,6H),1.19–1.82 (m,12H), 2.63–2.88 (m,3H), 3.08–3.9 (m,2H),4.26–4.42 (m) and 4.6–4.8 (m) and 5.23–5.44 (m) (2H),6.99–7.4 (m,4H)

Preparation 154

Boc-MeLeu-D-o-FPhLac-OH (1.03 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (1.45 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.05 (m,12H),1.18–1.83 (m,18H), 2.7–3.2 (m,8H), 4.6–4.8 (m) and 4.88–5.6 (m) (6H), 6.99–7.43 (m,9H)

FAB-MS: 601 [M-Boc+H]$^+$

Preparation 155

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.70 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.57 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.03 (m,12H),1.08–1.85 (m,18H), 2.59–3.38 (m,8H), 4.6–4.98 (m) and 5.05–5.6 (m) and 5.83–6.0 (m) (4H),6.99–7.38 (m,4H)

Preparation 156

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.61 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.53 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.62–1.03 (m,12H),1.2–2.05 (m,9H), 2.58–2.75 (m, 3H),2.98–3.36 (m,5H),3.62–3.82 (m,1H), 5.02–5.38 (m) and 5.46–5.63 (m) (5H),6.99–7.43 (m,9H)

Preparation 157

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.55 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.51 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.97 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$, δ): 0.78–1.04 (m,24H),1.10–1.82 (m,27H),2.7–3.23 (m,16H), 4.6–4.8 (m) and 5.02–5.61 (m) (10H),6.98–7.42 (m,13H)

FAB-MS: 1093 [M-Boc+H]$^+$

Preparation 158

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OBzl (0.89 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.84 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.78–1.05 (m,24H),1.12–1.82 (m,27H), 2.62–3.29 (m,16H), 4.5–5.87 (m,8H),6.98–7.38 (m,8H)

Preparation 159

(S)-3-fluorophenylaniline (5.20 g) was used instead of (S)-2-fluorophenylaniline. Except above matter, benzyl (S)-2-chloro-3-(3-fluorophenyl) propionate (7.04 g) was obtained according to a similar manner to that of Preparation 151.

NMR ($CDCl_3$,δ): 3.17 (dd,1H),3.36 (dd,1H)),4.47 (t,1H), 5.17 (s,2H),6.82–7.04 (m,3H),7.18–7.5 (m,6H)

EI-MS: 292 [M]$^+$

Preparation 160

Benzyl (S)-2-chloro-3-(3-fluorophenyl)propionate (1.76 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-m-FPhLac-OBzl (1.13 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.9 (d,6H),1.39–1.78 (m,12H),2.6–2.77 (m,3H),3.03–3.22 (m,2H),4.63–4.79 (m) and 4.92–5.36 (m) (4H),6.8–7.0 (m,3H), 7.18–7.42 (m,6H)

FAB-MS: 402 [M-Boc+H]$^+$

Preparation 161

Boc-MeLeu-D-m-FPhLac-OBzl (1.11 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-OH (1.00 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.82–1.00 (m,6H),1.2–1.8 (m,12H), 2.76–2.85 (m,3H), 3.02–3.25 (m,2H),4.38–4.5 (m) and 4.62–4.79 (m) and 5.19–5.41 (m) (2H),6.86–7.04 (m,3H), 7.19–7.38 (m,1H)

Preparation 162

Boc-MeLeu-D-m-FPhLac-OH (0.99 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.80–1.01 (m,12H),1.39–1.79 (m,18H), 2.73–3.18 (m,8H), 5.03–5.57 (m,6H),6.88–7.07 (m,3H), 7.21–7.42 (m,6H)

FAB-MS: 601 [M-Boc+H]$^+$

Preparation 163

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.69 g) was obtained according to a similar manner to that of

Preparation 25.

NMR CCDCl_3,δ): 0.8–1.02 (m,12H),1.1–1.8 (m,18H), 2.63–3.3 (m,8H), 4.62–5.59 (m) and 5.73–5.85 (m) (4H), 6.83–7.1 (m,3H),7.19–7.38 (m,1H)

Preparation 164

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.65 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.59 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.69–1.03 (m,12H),1.18–2.03 (m,9H), 2.58–2.7 (m,3H), 2.82–3.0 (m,3H),3.03–3.21 (m,2H), 3.62–3.82 (m,1H),5.01–5.38 (m) and 5.41–5.58 (m) (5H), 6.94–7.07 (m,3H),7.17–7.43 (m,6H)

Preparation 165

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.69 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, HCl.H-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (0.59 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OBzl (1.06 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.04 (m,24H),1.04–1.95 (m,27H), 2.6–3.3 (m,16H), 4.62–4.79 (m) and 4.88–5.58 (m) (10H), 6.82–7.14 (m,6H),7.19–7.42 (m,7H)

FAB-MS: 1094 [M-Boc+H]$^+$

Preparation 166

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-Do-m-FPhLac-MeLeu-D-Lac-OBzl (0.97 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter,

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.81 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.77–1.05 (m,24H),1.05–1.83 (m,27H), 2.58–3.22 (m,16H), 4.6–4.79 (m) and 4.88–5.78 (m) (8H), 6.85–7.08 (m,6H),7.18–7.39 (m,2H)

Preparation 167

(S)-4-fluorophenylaniline (5.00 g) was used instead of (S)-2-fluorophenylaniline. Except above matter, benzyl (S)-2-chloro-3-4-fluorophenyl) propionate (1.8 g) was obtained according to similar manner to that of Preparation 151.

NMR ($CDCl_3$,δ): 3.16 (dd,1H),3.33 (dd,1H),4.44 (t,1H), 5.15 (s,2H),6.88–7.42 (m,9H)

El-MS: 292 $[M]^+$

Preparation 168

Benzyl (S)-2-chloro-3-(4-fluorophenyl)propionate (2.21 g) was used instead of benzyl (S)-2-chloro-3-(4-methoxyphenyl) propionate. Except above matter, Boc-MeLeu-D-p-FPhLac-OBzl (1.55 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.9 (d,6H),1.3–1.62 (m,12H),2.58–2.67 (m,3H),3.0–3.12 (m,2H),4.6–4.79 (m) and 4.9–5.27 (m) (4H),6.9–7.42 (m,9H)

FAB-MS: 402 $[M\text{-}Boc+H]^+$

Preparation 169

Boc-MeLeu-D-p-FPhLac-OBzl (1.45 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-OH (1.25 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.83–1.00 (m,6H),1.41–1.78 (m,12H), 2.7–2.84 (m,3H), 3.02–3.23 (m,2H),4.41–5.39 (m,3H), 6.9–7.06 (m,2H),7.1–7.26 (m,2H)

Preparation 170

Boc-MeLeu-D-p-FPhLac-OH (1.23 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (2.06 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.7–1.04 (m,12H),1.1–1.97 (m,18H), 2.63–2.96 (m,6H), 3.0–3.18 (m,2H),4.6–5.5 (m,6H), 6.88–7.1 (m,2H),7.15–7.5 (m,7H)

FAB-MS: 601 $[M\text{-}Boc+H]^+$

Preparation 171

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.9 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.78 g) was obtained according to a similar manner to that of

Preparation 25.

NMR ($CDCl_3$,δ): 0.8–1.02 (m,12H),1.05–1.8 (m,18H), 2.62—3.3 (m,8H), 4.6–5.85 (m,4H),6.88–7.05 (m,2H), 7.12–7.28 (m,2H)

Preparation 172

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.89 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.85 g) was obtained according to a similar manner to that of Preparation 28.

NMR ($CDCl_3$,δ): 0.68–1.05 (m,12H),1.18–2.05 (m,9H), 2.53–2.68 (m,3H), 2.82–3.0 (m,3H),3.0–3.18 (m,2H), 3.63–3.81 (m,1H),5.02–5.38 (m,4H), 5.4–5.59 (m,1H), 6.96–7.07 (m,2H),7.15–7.42 (m,7H)

Preparation 173

Boc-MeLeu-D -p-FPhLac-MeLeu-D-Lac-OH (0.77 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (0.84 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.78–1.07 (m,24H),1.13–1.9 (m,27H), 2.62–3.28 (m,16H), 4.6–4.8 (m) and 4.9–5.57 (m) (10H), 6.86–7.07 (m,4H),7.07–7.42 (m,9H)

FAB-MS: 1094 $[M\text{-}Boc+H]^+$

Preparation 174

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OBzl (1.31 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.99 g) was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.79–1.05 (m,24H),1.18–1.93 (m,27H), 2.62–3.24 (m,16H), 4.58–5.8 (m,8H),6.88–7.04 (m,4H), 7.1–7.38 (m,4H)

Preparation 175

Boc-MeLeu-D)-p-MeOPhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.42 g) was used instead of, HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.28 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.77–1.02 (m,24H),1.02–1.96 (m,27H), 2.6–3.25 (m,16H), 3.78 (s,3H),4.6–4.8 (m) and 4.95–5.57 (m) (10H),6.78–6.90 (m,2H), 7.04–7.4 (m,12H)

FAB-MS: 1087 $[M\text{-}Boc+H]^+$

Preparation 176

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OBzl (1.13 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OH (0.98 g)was obtained according to a similar manner to that of Preparation 25.

NMR ($CDCl_3$,δ): 0.72–1.04 (m,24H),1.04–1.9 (m,27H), 2.6–3.25 (m,16H), 3.78 (s,3H),4.58—4.8 (m) and 4.82–5.56 (m) and 5.65–5.82 (m) (8H),6.78–6.9 (m,2H),7.03–7.38 (m,7H)

Preparation 177

Benzyl chloroacetate (1.85 g) was used instead of benzyl (S)- 2-chloro-3-(4-methoxyphenyl)propionate. Except above matter, Boc-MeLeu-Glycol-OBzl (4.0 g) was obtained according to a similar manner to that of Preparation 2.

NMR ($CDCl_3$,δ): 0.93 (d,6H),1.45 (s,9H),1.4–1.8 (m,3H),2.78 (s) and 2.80 (s) (3H),4.6–5.0 (m,3H),5.29 (s,2H),7.35 (s,5H)

IR (KBr): 1740,1695 cm^{-1}

Preparation 178

Boc-MeLeu-Glycol-OBzl (1.50 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-Glycol-OBzl (1.32 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1753 cm^{-1}

Preparation 179

Boc-MeLeu-D-p-MeOPhLac-OH (0.69 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-Glycol-OBzl (0.59 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.79 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.0 (m,12H),1.2–1.8 (m,6H),1.42 (s) and 1.47 (s) (9H),2.7–3.0 (m,6H),3.03 (d,2H),3.78

(s,3H),4.66 (s,2H),4.6–5.5 (m, 3H),5.28 (s,2H),6.82 (d,2H), 7.14 (d,2H),7.3–7.4 (m,5H)

IR (KBr): 1740,1694,1664 cm^{-1}

APCI-MS: 599 $[M+H]^+$

Preparation 180

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.32 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): 1744,1691,1663 cm^{-1}

Preparation 181

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.39 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.38 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1745,1653 cm^{-1}

Preparation 182

trifluoroacetic acid (2 ml) and stirred for 2 hours successively. The solvent was evaporated in vacuo, and the residue was dissolved in dioxane (30 ml). After adding the mixture dropwise for 5 hours into pyridine (629 ml) which was heated at 90° C., it was stirred for 2 and ½ hours successively. The solvent was evaporated in vacuo, azeotroped by toluene (30 ml). To the residue was added ethyl acetate (200 ml), washed with 10% aqueous citric acid solution, water, aqueous saturated sodium bicarbonate solution, water in order, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resultant crude product was purified by silica gel chromatography, and eluted with mixture of ethyl acetate and hexane (1.5:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MeOPhLac-MeLeu—D-Lac-MeLeu—D-p-MeOPhLac-MeLeu—D-Lac

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.32 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OH, and HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.37 g) was used instead of HCl.H-MeLeu-D-Lac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.603 g) was obtained according to a similar manner to that of Preparation 26.

NMR ($CDCl_3$,δ): 0.8–1.05 (m,24H),1.41 (s) and 1.47 (s) (9H),1.21–1.9 (m,12H),2.65–3.1 (m,16H),3.78 (s,6H), 4.60–4.85 (m) and 5.15– 5.5 (m) (10H),5.16 (s,2H), 6.75–6.90 (m,2H),7.05–7.2 (m,2H),7.3–7.4 (m,5H)

IR (KBr): 1744,1689,1667 cm^{-1}

(0.16 g).

NMR ($CDCl_3$,δ): 0.79–1.00 (m,24H), 1.10–1.80 (m,18H), 2.73–3.09 (m,16H), 3.78 (s,6H), 4.40–4.54 (m), and 5.00–5.67 (m) (8H), 6.82 (d, 4H), 7.15 (d,4H).

IR (KBr): 1741,1662 cm^{-1}

FAB-MS: 1009 $(M+H)^+$

EXAMPLE 2

Boc-MeLeu-D-Man-MeLeu-D-Lac-MeLeu-D-Man-MeLeu-D-Lac-OC $_6F_5$ was used instead of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OC_6F_5. Except above matter,

MeLeu—D-Man-MeLeu—D-Lac-MeLeu—D-Man-MeLeu—D-Lac

FAB-MS: 1189M+H]$^+$

Preparation 183

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OBzl (0.58 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-OBzl. Except above matter, Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.55 g) was obtained according to a similar manner to that of Preparation 25.

IR (KBr): **1742, 1664**cm^{-1}

Preparation 184

Boc-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.55 g) was used instead of Boc-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OBzl. Except above matter, HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.53 g) was obtained according to a similar manner to that of Preparation 28.

IR (KBr): 1741,1646 cm^{-1}

EXAMPLE 1

To a solution of Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-OC $_6F_5$ (0.4 g) in methylene chloride (4 ml) was added under ice-cooling,

(0.11 g) was obtained according to a similar manner to that of Example 1.

NMR ($CDCl_3$,δ): 0.70–1.00 (m,24H), 1.10–1.98 (m,18H), 2.75–3.10 (m,12H),4.60–5.70 (m,6H), 6.44 (s,2H),7.30–7.60 (m,10H).

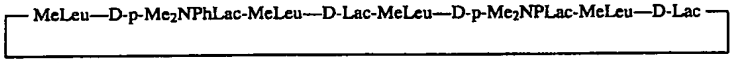
IR (KBr): 1750,1677 cm^{-1},

FAB-MS: 921 $(M+H)^+$

EXAMPLE 3

To a solution of 3HCl.H-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-MeLeu-D-p-Me_2NPhLac-MeLeu-D-Lac-OH (0.825 g) in dichloromethane was (700 ml) was added under ice-cooling, triethylamine (0.45 ml) and bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.27 g), and stirred for 14 hours successively, and further stirred for 4 hours at room temperature. The solvent was evaporated in vacuo, was added water (50 ml), and extracted with ethyl acetate (40 ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate and ethanol (60:35:5, v/v). The

fractions containing the desired product were combined and evaporated in vacuo to obtain



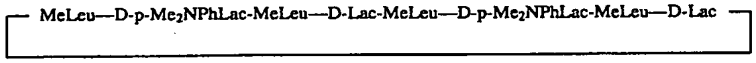
(0.40 g).

NMR ($CDCl_3$,δ) 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m,28H), 4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

FAB-MS: 1035 $[M+H]^+$

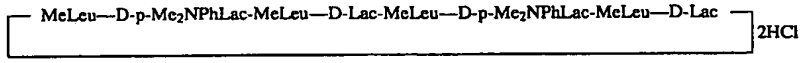
EXAMPLE 4



(0.145 g)

was dissolved in 4N-hydrogen chloride in ethyl acetate (2 ml).

The solvent was evaporated in vacuo, the residue was dissolved in 4N-hydrogen chloride in ethyl acetate (2 ml) again. After the solvent was evaporated in vacuo, azeotroped by toluene (10 ml) twice to give



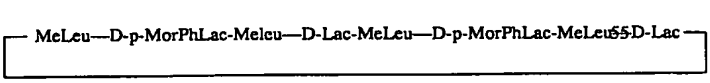
(0.157 g).

NMR ($CDCl_3$,δ) 0.7–1.1 (m,24H),1.25–1.85 (m,18H), 2.8–3.4 (m,16H), 3.15 (bs,12H),4.6–5.75 (m,8H),7.35–7.5 (m,4H),7.6–7.75 (m,4H)

IR (KBr): 1742,1649 cm^{-1}

EXAMPLE 5

To a solution of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH (0.404 g) in dichloromethane (162 ml) were added sodium bicarbonate (0.27 g) and bis(2-oxo-3-oxazolidinyl) phosphinic chloride (0.13 g), and stirred for 71 hours successively. The solvent was evaporated in vacuo, added water (50 ml), and extracted with ethyl acetate (50ml×3). The ethyl acetate layer was washed with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate, and ethanol (50:45:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain



(0.238 g).

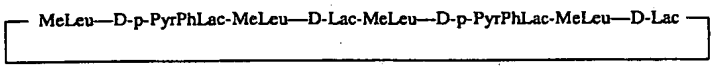
NMR ($CDCl_3$,δ) 0.8–1.1 (m,24H),1.3–1.8 (m,18H), 2.7–3.2 (m,24H), 3.8–3.9 (m,8H),44–4.55 (m) and 5.0–5.7 (m) (8H),6.82 (d,4H),7.13 (d, 4H)

IR (KBr): 1740, 1662 cm^{-1}

FAB-MS : 1119 $[M+H^+]$

EXAMPLE 6

3HCl.H-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-MeLeu-D-p-PyrPhLac-MeLeu-D-Lac-OH (0.80 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,



(0.238 g) was obtained according to a similar manner to that of

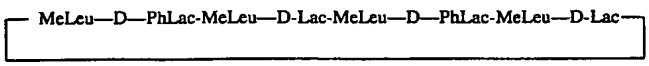
EXAMPLE 5.

NMR ($CDCl_3$,δ) 0.75–1.1 (m,24H),1.2–1.8 (m,18H), 1.9–2.05 (m,8H), 2.7–3.1 (m,16H),3.15–3.3 (m,8H), 4.4–4.55 (m) and 5.0–5.7 (m) (8H), 6.46 (d,4H),7.06 (d,4H)

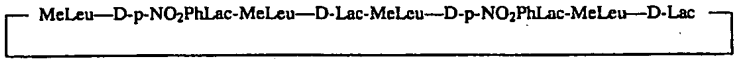
IR (KBr): 1740,1664 cm^{-1}

FAB-MS: 1087 $[M+H]^+$

EXAMPLE 7



(0.382 g) was cooled down to −10° C. After fuming nitric acid (3.5 ml) was added dropwise in 15 minutes, the mixture was stirred for one hour at room temperature. The reaction solution was added gradually into saturated sodium bicarbonate (25 ml), and extracted with ethyl acetate (25 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo to give crude product of



(0.465 g).

NMR ($CDCl_3$; δ) 0.65–1.1 (m,24H),1.2–1.8 (m,18H), 2.7–3.3 (m,16H), 44–4.55 (m) and 5.0–5.7 (m) (8H), 7.35–7.55 (m,4H),8.05–8.15 (m, 4H)

IR (KBr): 1742,1662,1519,1343 cm^{-1}

FAB-MS: 1039 $[M+H]^+$

EXAMPLE 8

To a ethanol (5 ml) solution of crude product (72 mg) of

MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac

were added 37% aqueous formaldehyde (0.4 ml) and 10% palladium on carbon (0.1 g), and hydrogenated for 2 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate and ethanol (75:20:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-Me_2NPhLac-MeLeu—D-Lac-MeLeu—D-p-Me_2NPhLac-MeLeu—D-Lac

(42 mg).

NMR ($CDCl_3$; δ) 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m,28H), 4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

EXAMPLE 9

To a methanol (10 ml) solution of crude product (312 mg) of

MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NO_2PhLac-MeLeu—D-Lac

was added 10% palladium on carbon (0.1 g), and hydrogenated for 2 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate and ethanol (40:55:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(144 mg).

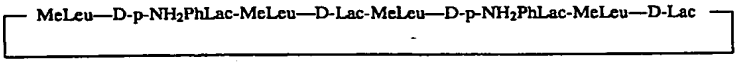
NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.4–1.85 (m,18H), 2.7–3.1 (m, 16H),4.4–5.8 (m,8H),6.64 (d,4H),7.08 (d,4H)

IR (KBr): 1741,1662 cm^{-1}

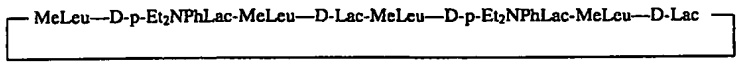
FAB-MS: 979 $[M+H]^+$

EXAMPLE 10

To a methanol (10 ml) solution of



(250 mg) were added acetaldehyde (0.56 g) and 10% palladium on carbon (0.15 g), and hydrogenated for 4 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (25:20:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain



(147 mg).

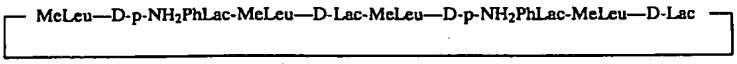
NMR ($CDCl_3$,δ): 0.7–1.9 (m,54H),2.65–3.1 (m,12H), 3.2–3.4 (m,8H), 4.4–4.5 (m) and 5.0–5.8 (m) (8H),6.45–6.6 (m,4H),7.0–7.1 (m,4H)

IR (KBr):1741,1662 cm^{-1}

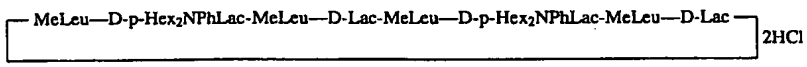
FAB-MS: 1091 $[M+H]^+$

EXAMPLE 11

To a methanol (10 ml) solution of



(250 mg) were added n-hexanal (0.62 g) and 10% palladium on carbon (0.15 g), and hydrogenated for 11 hours at room temperature under hydrogen gas atmospheric pressure. The catalyst was filtered off and the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (25:70:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo. To the resultant residue was added 4N-hydrogen chloride in ethyl acetate (5 ml), and the solvent was evaporated, repeated the same procedure again to give



(147 mg).

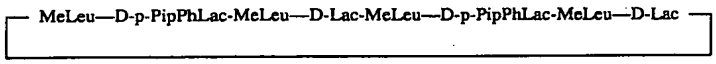
NMR ($CDCl_3$,δ): 0.7–2.1 (m,86H),2.7–3.6 (m,24H), 4.4–4.6 (m) and 5.0–5.7 (m) (8H),7.3–7.45 (m,4H),7.6–7.75 (m,4H)

IR (KBr): 1743,1656 cm^{-1}

FAB-MS: 1315 $[M+H]^+$

EXAMPLE 12

3HCl.H-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-MeLeu-D-p-PipPhLac-MeLeu-D-Lac-OH (1.24 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,



(0.82 g) was obtained according to a similar manner to that of Example 5.

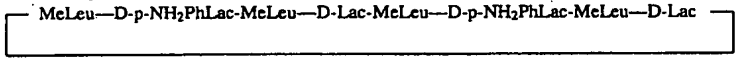
NMR ($CDCl_3$,δ): 0.7–1.1 (m,24H),1.2–1.9 (m,30H), 2.65–3.2 (m,24H), 4.4–4.55 (m) and 5.0–5.7 (m) (8H),6.84 (d,4H),7.09 (d,4H)

IR (KBr): 1740,1663 cm^{-1}

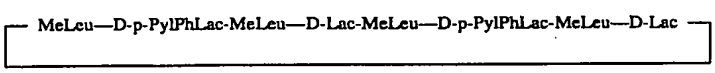
FAB-MS: 1115 $[M+H]^+$

EXAMPLE 13

A suspension of



(0.228 g),2,5-dimethoxytetrahydrofuran (0.045 ml) and acetic acid (1 ml) were stirred for 3 hours at room temperature, and further stirred for 3 hours at 50° C. Further more, to the mixture was added 2,5-dimethoxytetrahydrofuran (0.045 ml) and stirred for 3 hours successively. The reaction solution was poured into ice-aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate (20 ml×2). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (50:45:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain



(56.6 mg).

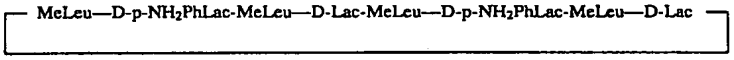
NMR ($CDCl_3$,δ): 0.77–1.1 (m,24H),1.2–1.82 (m,18H), 2.7–3.23 (m, 16H),52–5.73 (m,8H),6.28–6.39 (m,4H), 6.56–6.7 (m,4H),6.96–7.38 (m, 8H)

IR (KBr): 1742,1663 cm^{-1}

FAB-MS: 1079 $[M+H]^+$

EXAMPLE 14

To a trifluoroacetic acid (0.5 ml) solution of



(48 mg) was added at room temperature, sodium nitrite (8 mg), after the reaction solution was stirred for 1 hour at 60° C., the solvent was evaporated in vacuo and the residue was azeotroped by toluene. To the residue were added sodium bicarbonate (84 mg), water (0.5 ml), dioxane (2.5 ml) and after the mixture was stirred for 15 hours at room temperature, water (50 ml) was added and extracted with ethyl acetate (25 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (65:30:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(40.4 mg).

NMR ($CDCl_3$,δ): 0.70–1.8 (m,42H),2.7–3.15 (m,16H), 4.38–4.55 (m) and 4.97–5.68 (m) (8H),6.65–6.83 (m,4H), 6.94–7.17 (m,4H)

IR (KBr): 1741,1648 cm^{-1}

FAB-MS: 981 $[M+H]^+$

EXAMPLE 15

A suspension of

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(0.3 g), dimethylformamide (2 ml), potassium carbonate (128.5 mg) and ethyl iodide (0.08 ml) were stirred for 18 hours at room temperature, and then water (30 ml) was added and extracted with ethyl acetate (20 ml×3). After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane and ethyl acetate (1:1, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-EtOPhLac-MeLeu—D-Lac-MeLeu—D-p-EtOPhLac-MeLeu—D-Lac

(0.188 g).

NMR ($CDCl_3$,δ): 0.76–1.09 (m,24H),1.3–1.82 (m,16H), 2.7–3.15 (m, 16H),3.99 (q,4H),4.4–4.58 (m) and 4.9–5.8 (m) (8H),6.76–6.88 (m,4H), 7.07–7.39 (m,4H)

IR (KBr): 1743,1664 cm^{-1}

FAB-MS: 1037 $[M+H]^+$

EXAMPLE 16

n-Hexyl bromide (0.25 ml) was used instead of ethyl iodide. Except above matter,

MeLeu—D-p-HexOPhLac-MeLeu—D-Lac-MeLeu—D-p-HexOPhLac-MeLeu—D-Lac

(0,179 g) was obtained according to a similar manner to that of Example 15.

NMR ($CDCl_3$,δ): 0.70–1.9 (m,64H),2.68–3.2 (m,16H), 3.91 (t,4H),4.42–4.56 (m) and 5.03–5.9 (m) (8H),6.69–6.84 (m,4H),7.05–7.2 (m,4H)

IR (KBr): 1742,1661 cm^{-1}

FAB-MS: 1149 $[M+H]^+$

EXAMPLE 17

To Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH (1.03 g) was added 4N-hydrogen chloride in ethyl acetate solution (20 ml), and stirred for 50 minutes at 0° C. After the solvent was evaporated in vacuo, the residue was azeotroped by toluene, was added dichloromethane (850 ml), cooled down to 0° C., added triethylamine (0.47 ml) and bis (2-oxo-3-oxazolidinyl) phosphinic chloride (0.32 g), and stirred for 14 hours successively. The solvent was evaporated in vacuo, was added 5% citric acid (100 ml) and extracted with ethyl acetate (100 ml×2). After washing the ethyl acetate layer with aqueous saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography, eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (60:35:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MEPhLac-MeLeu—D-Lac-MeLeu—D-p-MEPhLac-MeLeu—D-Lac

(0.506 g).

NMR ($CDCl_3$,δ): 0.78–1.08 (m,24H),1.2–1.9 (m,18H), 2.62–3.09 (m, 16H),3.45 (s,6H),3.65–3.82 (m,4H), 4.02–4.19 (m,4H),4.6–4.78 (m) and 5.01–5.7 (m) (8H), 6.8–6.96 (m,4H),7.12–7.22 (m,4H)

IR (KBr): 1740,1662 cm^{-1}

FAB-MS: 1097 $[M+H]^+$

EXAMPLE 18

A suspension of

MeLeu—D-p-OHPhLac-MeLeu—D-Lac-MeLeu—D-p-OHPhLac-MeLeu—D-Lac

(0.3 g), dimethylformamide (2 ml), potassium carbonate (128.5 mg),1-bromo- 2-(2-methoxyethoxy)ethane (0.93 ml), and sodium iodide (92.9 mg) were stirred for 17 hours at room temperature and stirred for 24 hours at 50° C. Further, to the mixture was added sodium iodide (92.9 mg) and stirred for 8 hours successively. To the mixture was added water (30 ml) and extracted with ether (20 ml×3). After washing the ether layer with saturated brine, dried over anhydrous sodium sulfate, the crude product which was gained by evaporating the solvent was purified by silica gel column chromatography and eluting with a mixed solvent of hexane, ethyl acetate, and ethanol (30:65:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MEEPhLac-MeLeu—D-Lac-MeLeu—D-p-MEEPhLac-MeLeu—D-Lac

(0.105 g).

NMR ($CDCl_3$,δ): 0.71–1.82 (m,54H),2.84–3.23 (m,16H), 3.39 (s,6H), 3.59–3.63 (m,4H),3.63–3.79 (m,4H),3.79–3.92 (m,4H),4.03–4.2 (m,4H), 4.39–4.56 (m) and 5.0–5.77 (m) (8H),6.83 (d,4H),7.13 (d,4H)

IR (KBr): 1743,1662 cm^{-1}

FAB-MS: 1185 $[M+H]^+$

EXAMPLE 19

Boc-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-MeLeu-D-o-MeOPhLac-MeLeu-D-Lac-OH (1.24 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-o-MeOPhLac-MeLeu—D-Lac-MeLeu—D-o-MeOPhLac-MeLeu—D-Lac

(0.87 g) was obtained according to a similar manner to that of EXAMPLE 17.

NMR ($CDCl_3$,δ): 0.79–1.08 (m,24H),1.20–1.81 (m,18H), 2.71–3.15 (m, 16H),3.85 (s) and 3.86 (s) (6H),4.40–5.89 (m,8H),6.82–6.93 (m,4H),7.12–7.27 (m,4H)

IR (KBr):**1741,1663**cm^{-1}

FAB-MS: 1009 $[M+H]^+$

MeLeu—D-2,4-DMOPhLac-MeLeu—D-Lac-MeLeu—D-2,4-DMO—PhLac-MeLeu—D-Lac

EXAMPLE 20

Boc-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-MeLeu-D-m-MeOPhLac-MeLeu-D-Lac-OH (0.79 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-m-MeOPhLac-MeLeu—D-Lac-MeLeu—D-m-MeOPhLac-MeLeu—D-Lac

(0.51 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.75–1.15 (m,24H),1.20–1.85 (m,18H), 2.70–3.18 (m, 16H),3.78 (s,6H),4.40–5.78 (m,8H), 6.70–6.88 (m,6H),7.10–7.25 (m,2H)

IR (KBr):**1739,1661**cm^{-1}

FAB-MS: 1009M+H]$^+$

EXAMPLE 21

Boc-MeLeu-D-3,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D- 3,4-DMOPhLac-MeLeu-D-Lac-OH (0.26 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-3,4-DMOPhLac-MeLeu—D-Lac-MeLeu—D-3,4-DMO—PhLac-MeLeu—D-Lac

(0.14 g) was obtained according to a similar manner to that of EXAMPLE 17.

MeLeu—D-3,4-MODPhLac-MeLeu—D-Lac-MeLeu—D-3,4-MODPhLac-MeLeu—D-Lac

NMR ($CDCl_3$,δ): 0.72–1.00 (m,24H),1.21–1.80 (m,18H), 2.72–3.15 (m, 16H),3.85 (s,6H),3.86 (s,6H),4.42–5.72 (m,8H),6.72–6.81 (m,6H)

IR (KBr): 1740,1661 cm^{-1}

FAB-MS: 1069 $[M+H]^+$

EXAMPLE 22

Boc-MeLeu-D-2,4-DMOPhLac-MeLeu-D-Lac-MeLeu-D- 2,4-DMOPhLac-MeLeu-D-Lac-OH (1.49 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

(0.95 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.78–1.12 (m,24H),1.20–1.80 (m,18H), 2.70–3.16 (m, 16H),3.75–3.90 (m,12H),4.40–5.83 (m,8H), 6.35–6.43 (m,4H),7.01–7.12 (m,2H)

IR (KBr): 1740,1661 cm^{-1}

FAB-MS: 1069 $[M+H]^+$

EXAMPLE 23

Boc-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-MeLeu-D-3,4-MODPhLac-MeLeu-D-Lac-OH (0.59 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

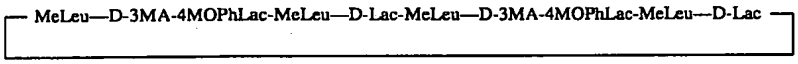
(0.29 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.80–1.12 (m,24H),1.22–2.00 (m,18H), 2.63–3.20 (m, 16H),4.35–4.53 (m) and 5.00–5.70 (m) (8H), 5.82–6.00 (m,4H),6.60–6.82 (m,6H)

IR (KBr):1740,1661 cm^{-1}
FAB-MS: 1037 $[M+H]^+$

EXAMPLE 24

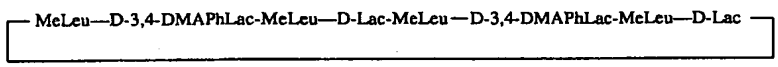
3HCl.H-MeLeu-D-3MA-4MOPhLac-MeLeu-D-Lac-MeLeu-D- 3MA-4MOPhLac-MeLeu-D-Lac-OH (1.18 g) was used instead of 3HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,



(0.390 g) was obtained according to a similar manner to that of Example 5.
NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.2–2.1 (m,18H), 2.6–3.3 (m,28H), 3.85 (s,6H),4.4–4.55 (m) and 5.0–5.7 (m) (8H),67–6.9 (m,6H)
IR (KBr):1741,1663 cm^{-1}
FAB-MS: 1095 $[M+H]^+$

EXAMPLE 25

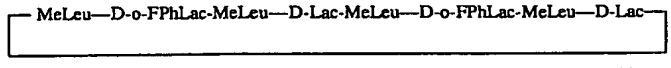
Boc-MeLeu-D-3,4-DMAPhLac-MeLeu-D-Lac-MeLeu-D- 3,4-DMAPhLac-MeLeu-D-Lac-OH (0.35 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH, and N-methylmorpholine (0.186 ml) was used instead of triethylamine. Except above matter,



(0.19 g) was obtained according to a similar manner to that of Example 17.
NMR ($CDCl_3$,δ): 0.70–1.10 (m,24H),1.15–1.90 (m,18H), 2.68–3.20 (m,40H),4.39–4.60 (m) and 4.95–5.75 (m) (8H), 6.65–6.80 (m,6H)
IR (KBr):1739,1662 cm^{-1}
FAB-MS: 1121 $[M+H]^+$

EXAMPLE 26

Boc-MeLeu-D-o-FPhLac-MeLeu-D-Lac-MeLeu-D-o-FPhLac-MeLeu-D-Lac-OH (0.82 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,



(0.58 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.64–1.13 (m,24H),1.21–1.83 (m,18H), 2.63–3.22 (m,16H),4.4–4.57 (m) and 5.02–5.82 (m) (8H), 6.98–7.38 (m,8H)

IR (KBr): 1743,1663 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 27

Boc-MeLeu-D-m-FPhLac-MeLeu-D-Lac-MeLeu-D-m-FPhLac-MeLeu-D-Lac-OH (0.77 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-m-FPhLac-MeLeu—D-Lac-MeLeu—D-m-FPhLac-MeLeu—D-Lac

(0.534 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.7–1.06 (m,24H),1.1–1.95 (m,18H), 2.6–3.27 (m,16H),4.4–4.58 (m) and 5.0–5.78 (m) (8H), 6.82–7.1 (m,6H),7.18–7.38 (m,2H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 28

Boc-MeLeu-D-p-FPhLac-MeLeu-D-Lac-MeLeu-D-p-FPhLac-MeLeu-D-Lac-OH (0.99 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-FPhLac-MeLeu—D-Lac-MeLeu—D-p-FPhLac-MeLeu—D-Lac

(0.686 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.7–1.1 (m,24H),1.18–1.9 (m,18H), 2.62–3.23 (m,16H),4.4–4.58 (m) and 5.0–5.75 (m) (8H), 6.89–7.07 (m,4H),7.07–7.25 (m,4H)

IR (KBr): 1741,1662 cm^{-1}

FAB-MS: 985 $[M+H]^+$

EXAMPLE 29

Boc-MeLeu-D-p-MeOPhLac-MeLeu-D-Lac-MeLeu-D-PhLac-MeLeu-D-Lac-OH (0.96 g) was used instead of Boc-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-MeLeu-D-p-MEPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-MeOPhLac-MeLeu—D-Lac-MeLeu—D-PhLac-MeLeu—D-Lac

(0.461 g) was obtained according to a similar manner to that of Example 17.

NMR ($CDCl_3$,δ): 0.78–1.06 (m,24H),1.3–1.82 (m,18H), 2.64–3.21 (m,16H),3.78 (s,3H),4.6–4.78 (m) and 5.02–5.8 (m) (8H),6.78–6.93 (m,2H),7.1–7.4 (m,7H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 979 $[M+H]^+$

EXAMPLE 30

HCl.H-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-MeLeu-D-p-MeOPhLac-MeLeu-Glycol-OH (0.52 g) was used instead of HCl.H-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-MeLeu-D-p-MorPhLac-MeLeu-D-Lac-OH. Except above matter,

MeLeu—D-p-MeOPhLac-MeLeu-Glycol-MeLeu—D-MeOPhLac- MeLeu-Glycol

(0.26 g) was obtained according to a similar manner to that of Example 5.

NMR ($CDCl_3$,δ): 0.75–1.1 (m,24H),1.2–1.8 (m,12H), 2.7–3.2 (m,16H), 3.78 (s,3H),3.79 (s,3H),42–5.8 (m,10H), 6.75–6.9 (m,4H),7.05–7.2 (m,4H)

IR (KBr): 1741,1663 cm^{-1}

FAB-MS: 981 $[M+H]^+$

EXAMPLE 31

To an aqueous suspension (5 ml) of oxydiacetaldehyde bis(diethylacetal) (0.50 g) was added five drops of acetic acid and heated for half an hour at 100° C. To the resultant oxydiacetaldehyde solution was added acetonitrile solution (5 ml) of

MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac-MeLeu—D-p-NH_2PhLac-MeLeu—D-Lac

(0.198 g) and after stirring for half an hour at room temperature, adjusted to pH7.0 by aqueous saturated sodium bicarbonate solution. To the mixture was added sodium cyanoborohydride (0.055 g) and pH was kept under 7.5 with acetic acid and in the meanwhile, it was stirred for 2 hours at room temperature. To the resultant reaction solution was added water (50 ml) and aqueous saturated sodium bicarbonate solution (5 ml), and extracted with ethyl acetate. After washing the ethyl acetate layer with saturated brine, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the resultant crude product was purified by silica gel chromatography, and eluted with mixture of hexane, ethyl acetate, and ethanol (55:40:5, v/v). The fractions containing the desired product were combined and evaporated in vacuo to obtain

MeLeu—D-p-MorPhLac-MeLeu—D-Lac-MeLeu—D-p-MorPhLac-MeLeu—D-Lac

(0.045 g).

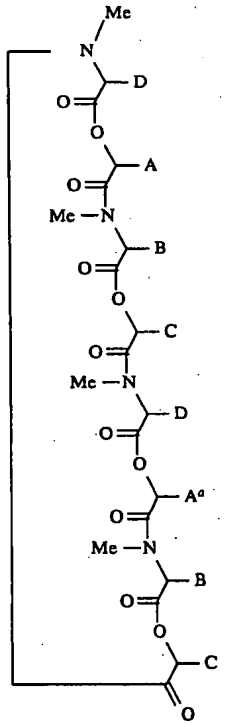
NMR ($CDCl_3$,δ): 0.8–1.1 (m,24H),1.3–1.8 (m,18H), 2.7–3.2 (m,24H), 3.8–3.9 (m,8H),4.4–4.55 (m) and 5.0–5.7 (m) (8H),6.82 (d,4H),7.13 (d, 4H)

IR (KBr): 1740,1662 cm^{-1}

FAB-MS: 1119 $[M+H]^+$

What we claim is:

1. A compound of the general formula (I):



(I)

wherein

A is a substituted benzyl group or a phenyl group which may have substituent(s),

A^a is a benzyl group which may have substituent(s) or a phenyl group which may have substituent(s),

B and D are each lower alkyl, and

C is hydrogen or lower alkyl,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by cyclic amino, dilower alkylamino or lower alkoxy,

B and D are each isopropyl, and

C is methyl.

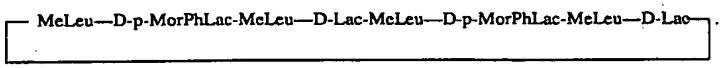
3. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by morpholino, dimethylamino or methoxy.

4. A compound of claim 1, wherein A and A^a are each a benzyl group substituted by amino, nitro or hydroxy,

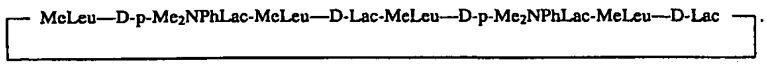
B and D are each isopropyl, and

C is methyl.

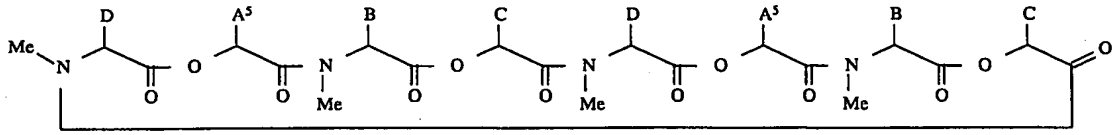
5. A compound of the formula:



6. A compound of the formula:

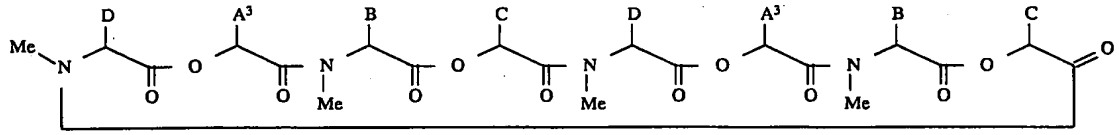


7. A process for preparation of a compound of the general formula:



or a salt thereof, which comprises

subjecting a compound of the general formula:



or a salt thereof, to a monoalkylation reaction followed by an intramolecular reaction,

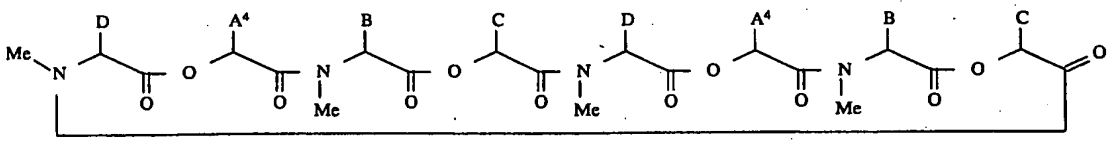
wherein B and D are each lower alkyl,

C is hydrogen or lower alkyl,

A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and

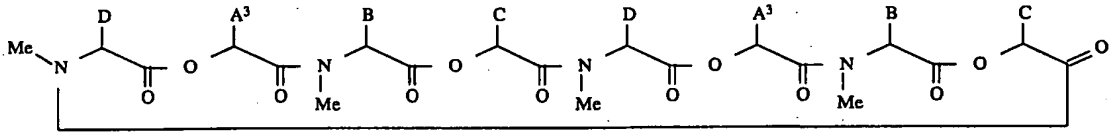
A^5 is a benzyl group substituted by cyclic amino, or a benzyl group substituted by cyclic amino and lower alkoxy.

8. A process for preparation of a compound of the general formula:



or a salt thereof, which comprises

subjecting a compound of the general formula:



or a salt thereof, to an alkylation reaction,

wherein B and D are each lower alkyl,

C is hydrogen or lower alkyl,

A^3 is a benzyl group substituted by amino, or a benzyl group substituted by amino and lower alkoxy, and

A^4 is a benzyl group substituted by mono- or di-lower alkylamino, or a benzyl group substituted by mono- or di-lower alkylamino and lower alkoxy.

9. An anthelmintic agent which comprises a compound or a pharmaceutically acceptable salt thereof of claim **1** as an active ingredient.

10. The compound of claim **1** wherein B and D are each an isobutyl group.

11. The compound of claim **1** wherein A and A^a are each a benzyl group substituted by a para-methoxy group.

12. The process of claim **7** wherein B and D are each an isobutyl group.

* * * * *

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUST
1940 DUKE STREET
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,514,773	**$940.00**	**$0.00**	**11/01/99**	**08/295,782**	**05/07/96**	**09/12/94**	**04**	**NO**	**188590PCT**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 22850 ISTMT DATE PRINTED 08/25/2007

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MAINTENANCE FEE STATEMENT

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,514,773	**$2,090.00**	**$0.00**	**10/07/03**	**08/295,782**	**05/07/96**	**09/12/94**	**08**	**NO**	**188590PCT**

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DEPSIPEPTIDE DERIVATIVE, PRODUCTION THEREOF AND USE THEREOF

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☐ was filed as PCT international application

Number PCT/JP93/00286

on March 8, 1993,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under Section 119 of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year	Priority Claimed
4-92070	Japan	17/03/92	☒ Yes ☐ No
4-305093	Japan	15/10/92	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, We (I) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number, 25,599; Arthur I. Neustadt, Registration Number 24,854; Robert C. Miller, Registration Number 25,357; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number, 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Stuart D. Dwork, Registration Number 31,103; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; William B. Walker, Registration Number 22,498; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Gilberto M. Villacorta, Registration Number 34,038; and John H.O. Clarke, Registration Number 17,373; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Hitoshi Nishiyama
NAME OF FIRST ~~SOLE~~ INVENTOR

Residence: 13-1-317, Kuzuharashinmachi, Neyagawa-shi, OSAKA 572 JAPAN

JPX

Hitoshi Nishiyama
Signature of Inventor

Citizen of: Japan

Post Office Address: the same as above

August 5, 1994
Date

2-00

Masaru Ohgaki
NAME OF SECOND JOINT INVENTOR

Masaru Ohgaki
Signature of Inventor

August 5, 1994
Date

Residence: 3-1-58-317, Minatojimanakamachi, Chuo-ku, Kobe-shi, HYOGO 572 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

3-00

Ryo Yamanishi
NAME OF THIRD JOINT INVENTOR

Ryo Yamanishi
Signature of Inventor

August 5, 1994
Date

Residence: 16-3, Hoshimi-cho, Ibaraki-shi, OSAKA 567 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

4-00

Toshihiko Hara
NAME OF FOURTH JOINT INVENTOR

Toshihiko Hara
Signature of Inventor

August 5, 1994
Date

Residence: 565-19, Ooaza Miyaji, Miura-mura, Inashiki-gun, IBARAKI 300-04 JAPAN JPX

Citizen of: Japan

Post Office Address: the same as above

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

STATEMENT

Assistant Commissioner for Patents
Alexandria, VA 22313-1450

Sir/Madam:

I, Katsunobu Ihara, of which postal address is ARK MORI BLDG, 13F, 12-32, Akasaka 1-chome, Minato-ku, Tokyo, Japan hereby state that:

I well understand the Japanese and English languages and attached is an accurate English translation made by me of the certified copy of the commercial register (Certificate of All the Records Registered) of Astellas Pharma Inc.

Date : July 1, 2005 Name : 井原 克誠

Katsunobu IHARA

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

Certificate of All the Records Registered

Trade name	Yamanouchi Pharmaceutical Co., Ltd.	
	Astellas Pharma Inc.	Changed April 1, 2005 Registered April 1, 2005
Location of head office	3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
Method of public notice	The statement is executed by publication in the *Nihon Keizai Shimbun* issued in Tokyo.	
Matters necessary for obtaining information relating to the balance sheet	http://www.yamanouchi.com/jp/index.html	Established March 25, 2003 Registered April 1, 2003
	http://www.astellas.com/jp	Changed April 1, 2005 Registered April 1, 2005
Date of incorporation	March 20, 1939	
Object	1. Manufacture, sale, import and export of pharmaceuticals, quasi-drugs, drugs used for animals, industrial chemicals, agricultural chemicals and other chemical products 2. Manufacture, sale, import and export of foods, food additives, seasonings, livestock feeds, feed additives, cosmetics, sanitary fixtures, medical instruments, meters and gauges, daily necessaries and miscellaneous goods 3. Manufacture, sale, import and export of medical machines and equipment, industrial machines and equipment and household equipment 4. Manufacture, sale, import and export of alcoholic beverages and other beverages 5. Breeding, sale, import and export of laboratory animals 6. Sale, purchase, lease, and management of real estate and agency business thereof 7. Warehouse business and road transport business 8. Hotel business, and management and control of health and physical education facilities and equipment 9. Casualty insurance agency business 10. Information processing service business using computer 11. All businesses incidental to or related to one of the preceding Items	
	1. Manufacture, sale, import and export of pharmaceuticals, quasi-drugs, drugs used for animals, reagents, industrial chemicals, agricultural chemicals and other chemical products 2. Manufacture, sale, import and export of foods, food additives, seasonings, fertilizers, livestock feeds, feed additives, cosmetics, sanitary fixtures, medical instruments, medical instruments used for animals, meters and gauges, daily necessaries and miscellaneous goods 3. Sale, purchase, import and export of natural products 4. Lease and maintenance of medical instruments 5. Manufacture, sale, import, export, lease and maintenance of medical machines and equipment, industrial machines and equipment and household equipment 6. Scientific inspections related to medical treatment 7. Manufacture, sale, import and export of liquors, alcoholic beverages and other beverages 8. Breeding, sale, import and export of laboratory animals 9. Sale, purchase, lease, and management of real estate and agency business thereof 10. Warehouse business, road transport business and freight transport business	

	11. Hotel business, and management and control of health and physical education facilities and equipment 12. Casualty insurance agency business 13. Publishing business 14. Sale, lease and maintenance of computer 15. Development, sale and lease of computer software 16. Information processing and information service business using computer 17. Management consulting business 18. All businesses incidental to or related to one of the preceding Items Changed April 1, 2005, and registered April 1, 2005	
Number of shares of one unit	1,000 shares	
	100 shares	Changed April 1, 2002 Registered April 2, 2002
Total number of shares authorized to be issued	800 million shares	
	2 billion shares	 Registered April 1, 2005
Total number of shares issued giving type of stock and number of shares of each type	Total number of issued shares 361,152,522 shares	Changed April 30, 2001 Registered May 9, 2001
	Total number of issued shares 361,203,052 shares	Changed February 28, 2002 Registered March 11, 2002
	Total number of issued shares 361,203,604 shares	Changed April 30, 2002 Registered May 10, 2002
	Total number of issued shares 361,214,262 shares	Changed May 31, 2002 Registered June 12, 2002
	Total number of issued shares 361,216,470 shares	Changed December 30, 2002 Registered January 14, 2003
	Total number of issued shares 361,221,523 shares	Changed April 30, 2004 Registered May 13, 2004
	Total number of issued shares 361,549,971 shares	Changed October 31, 2004 Registered November 10, 2004
	Total number of issued shares 361,954,215 shares	Changed January 31, 2005 Registered February 8, 2005
	Total number of issued shares 571,428,003 shares	 Registered April 1, 2005
Amount of capital	¥99,694,563,841	Changed April 30, 2001 Registered May 9, 2001
	¥99,744,563,841	Changed February 28, 2002 Registered March 11, 2002
	¥99,745,563,513	Changed April 30, 2002 Registered May 10, 2002
	¥99,756,563,185	Changed May 31, 2002 Registered June 12, 2002
	¥99,760,561,873	Changed December 30, 2002 Registered January 14, 2003
	¥99,765,561,873	Changed April 30, 2004 Registered May 13, 2004
	¥100,090,561,873	Changed October 31, 2004 Registered November 10, 2004
	¥100,490,561,873	Changed January 31, 2005 Registered February 8, 2005

*Underlined matters are underlined

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

Name, address, and place of business of transfer agent	33-1, Shiba 3-chome, Minato-ku, Tokyo The Chuo Mitsui Trust and Banking Company, Limited 33-1, Shiba 3-chome, Minato-ku, Tokyo Head Office, The Chuo Mitsui Trust and Banking Company, Limited Changed December 4, 2000, and registered December 8, 2000	
Matters relating to officers	Director Masayoshi Onoda	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Toichi Takenaka Director Toichi Takenaka	Reappointed June 28, 2001 Registered July 10, 2001 Reappointed June 27, 2003 Registered July 11, 2003 Resigned March 31, 2005 Registered April 1, 2005
	Director Kaoru Kimura	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Munetoshi Kakitani	Reappointed June 28, 2001 Registered July 10, 2001 Retired June 27, 2003 Registered July 11, 2003
	Director Nobuji Takayama Director Nobuji Takayama	Reappointed June 28, 2001 Registered July 10, 2001 Reappointed June 27, 2003 Registered July 11, 2003 Resigned March 31, 2005 Registered April 1, 2005
	Director Kiyoshi Kawaishi	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Hidehiko Ueda Director Hidehiko Ueda	Reappointed June 29, 2000 Registered July 12, 2000 Reappointed June 27, 2002 Registered July 10, 2002 Retired June 24, 2004 Registered July 7, 2004
	Director Hiroshi Suzuki	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Youzou Noura	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002
	Director Masakatsu Inoue	Reappointed June 29, 2000 Registered July 12, 2000 Retired June 27, 2002 Registered July 10, 2002

	Director Toshinari Tamura	Reappointed June 29, 2000
		Registered July 12, 2000
	Director Toshinari Tamura	Reappointed June 27, 2002
		Registered July 10, 2002
	Director Toshinari Tamura	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Director Kunihide Ichikawa	Reappointed June 29, 2000
		Registered July 12, 2000
	Director Kunihide Ichikawa	Reappointed June 27, 2002
		Registered July 10, 2002
	Director Kunihide Ichikawa	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Director Shigekazu Takahashi	Reappointed June 28, 2001
		Registered July 10, 2001
	Director Shigekazu Takahashi	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Kazuyoshi Hatanaka	Appointed June 29, 2000
		Registered July 12, 2000
	Director Kazuyoshi Hatanaka	Reappointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Yasuo Ishii	Appointed June 29, 2000
		Registered July 12, 2000
	Director Yasuo Ishii	Reappointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Toshio Saba	Appointed June 28, 2001
		Registered July 10, 2001
	Director Toshio Saba	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Isao Kishi	Appointed June 28, 2001
		Registered July 10, 2001
	Director Isao Kishi	Reappointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Hiroaki Hiraiwa	Appointed June 28, 2001
		Registered July 10, 2001
	Director Hiroaki Hiraiwa	Reappointed June 27, 2003
		Registered July 11, 2003

		Resigned June 24, 2004
		Registered July 7, 2004
	Director Isao Yanagisawa	Appointed June 28, 2001
		Registered July 10, 2001
	Director Isao Yanagisawa	Reappointed June 27, 2003
		Registered July 11, 2003
	Director Isao Yanagisawa	Family name of Isao Yanagisawa
		Modified March 19, 2004
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Shinji Usuda	Appointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Ikuya Sugisaki	Appointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Hajime Nakajima	Appointed June 27, 2002
		Registered July 10, 2002
		Retired June 24, 2004
		Registered July 7, 2004
	Director Iwaki Miyazaki	Appointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Kouji Yoshinaga	Appointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Tadao Hasegawa	Appointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Director Makoto Matsuo (is an outside director)	Appointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Director Hatsuo Aoki	Appointed April 1, 2005
		Registered April 1, 2005
	Director Toichi Takenaka	Appointed April 1, 2005
		Registered April 1, 2005
	Director Toshinari Tamura	Appointed April 1, 2005
		Registered April 1, 2005
	Director Masafumi Nogimori	Appointed April 1, 2005
		Registered April 1, 2005
	Director Kunihide Ichikawa	Appointed April 1, 2005
		Registered April 1, 2005
	Director Koichi Sejima	Appointed April 1, 2005
		Registered April 1, 2005

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

	Director Akiro Kojima (is an outside director)	Appointed April 1, 2005
		Registered April 1, 2005
	Director Makoto Matsuo (is an outside director)	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Masayoshi Onoda 931-35, Nonoshita 3-chome, Nagareyama-shi, Chiba	Reappointed June 28, 2001
		Registered July 10, 2001
		Resigned June 27, 2002
		Registered July 10, 2002
	Representative Director Toichi Takenaka 505-56, Matsugaoka 4-chome, Nagareyama-chi, Chiba	Reappointed June 28, 2001
		Registered July 10, 2001
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Changed address March 10, 2003
		Registered March 17, 2003
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Reappointed June 27, 2003
		Registered July 11, 2003
		Retired March 31, 2005
		Registered April 1, 2005
	Representative Director Hidehiko Ueda 3-2-1202, Nihonbashi Hamacho 2-chome, Chuo-ku, Tokyo	Appointed June 27, 2003
		Registered July 11, 2003
		Retired June 24, 2004
		Registered July 7, 2004
	Representative Director Toshinari Tamura 21-10, Midoricho 1-chome, Hasuda-shi, Saitama	Appointed October 1, 2004
		Registered October 1, 2004
		Retired March 31, 2005
		Registered April 1, 2005
	Representative Director Hatsuo Aoki 13-3, Hata 4-chome, Ikeda-shi, Osaka	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Toichi Takenaka 34-1-1405, Shiba 3-chome, Minato-ku, Tokyo	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Toshinari Tamura 21-10, Midoricho 1-chome, Hasuda-shi, Saitama	Appointed April 1, 2005
		Registered April 1, 2005
	Representative Director Masafumi Nogimori 65-2, Makamicho 6-chome, Takatsuki-shi, Osaka	Appointed April 1, 2005
		Registered April 1, 2005
	Auditor Hiroyuki Himaki	Appointed June 29, 2000
		Registered July 12, 2000
		Retired June 27, 2003
		Registered July 11, 2003
	Auditor Norio Sasaki	Appointed June 29, 2000
		Registered July 12, 2000
	Auditor Norio Sasaki	Reappointed June 27, 2003

		Registered July 11, 2003
		Retired March 31, 2005
		Registered April 1, 2005
	Auditor Shirou Tachikawa	Appointed June 29, 2000
		Registered July 12, 2000
		Retired June 27, 2003
		Registered July 11, 2003
	Auditor Toyomichi Ohtani	Appointed June 28, 2001
		Registered July 10, 2001
	Auditor Toyomichi Ohtani	Reappointed June 24, 2004
		Registered July 7, 2004
		Resigned March 31, 2005
		Registered April 1, 2005
	Auditor Hideo Yamada	Appointed June 28, 2001
		Registered July 10, 2001
	Auditor Hideo Yamada	Reappointed June 24, 2004
		Registered July 7, 2004
	Auditor Kenichirou Saitou	Appointed June 27, 2003
		Registered July 11, 2003
	Auditor Makoto Matsuo	Appointed June 27, 2003
		Registered July 11, 2003
		Resigned June 24, 2004
		Registered July 7, 2004
	Auditor Masaya Ishii	Appointed April 1, 2005
		Registered April 1, 2005
	Auditor Kanji Kobayashi	Appointed April 1, 2005
		Registered April 1, 2005
Branch office	1 4-7, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-7, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	Moved September 28, 2002
		Registered October 4, 2002
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 24, 2005
		Registered February 1, 2005
	2 7-12, Kitahama 3-chome, Chuo-ku, Osaka	
	6-5, Kawaramachi 3-chome, Chuo-ku, Osaka	Moved May 19, 2003
		Registered May 21, 2003
	3 9-1, Oodori-nishi 5-chome, Chuo-ku, Sapporo, Hokkaido	
	4 10-21, Sakae 1-chome, Naka-ku, Nagoya	
	1-36, Marunouchi 2-chome, Naka-ku, Nagoya	Moved April 1, 2005
		Registered April 1, 2005

*Deleted matters are underlined

	5 2-25, Oomachi 2-chome, Aoba-ku, Sendai, Miyagi	
	6 18-25, Hakataeki-higashi 1-chome, Hakata-ku, Fukuoka	
	2-1, Shimokawabata, Hakata-ku, Fukuoka	Moved April 1, 2005 Registered April 1, 2005
	7 5-6, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 31, 2005 Registered February 1, 2005
	24-8, Higashiueno 5-chome, Taito-ku, Tokyo	Moved April 1, 2005 Registered April 1, 2005
	8 4-8, Kotobukicho 1-chome, Takamatsu-shi, Kagawa	
	2-1, Sunport, Takamatsu-shi, Kagawa	Moved March 22, 2004 Registered March 22, 2004
	9 7-2, Otemachi 3-chome, Naka-ku, Hiroshima	
	11-10, Otemachi 2-chome, Naka-ku, Hiroshima	Moved April 1, 2005 Registered April 1, 2005
	10 287, Nanjing Donglu 3-duan, Taibei	
		Abolished October 31, 2004 Registered November 1, 2004
	11 84-2, Ohtamachi 6-chome, Naka-ku, Yokohama	
	2-1, Minatomirai 2-chome, Nishi-ku, Yokohama	Moved February 25 2003 Registered March 4, 2003
	12 513, Akinono-cho, Nijo-sagaru, Karasuma-dori, Nakagyo-ku, Kyoto	
	13 5-6, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo	
	5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Moved January 31, 2005 Registered February 1, 2005
	7-5, Sakuragicho 1-chome, Omiya-ku, Saitama	Moved April 1, 2005 Registered April 1, 2005

	15 2-25, Oomachi 2-chome, Aoba-ku, Sendai, Miyagi	Established April 1, 2005 Registered April 1, 2005
	16 24-8, Higashiueno 5-chome, Taito-ku, Tokyo	Established April 1, 2005 Registered April 1, 2005
	17 6, Nakase 2-chome, Mihama-ku, Chiba	Established April 1, 2005 Registered April 1, 2005
	18 5-9, Nihonbashi-Honcho 1-chome, Chuo-ku, Tokyo	Established April 1, 2005 Registered April 1, 2005
	19 1-36, Marunouchi 2-chome, Naka-ku, Nagoya	Established April 1, 2005 Registered April 1, 2005
	20 5-2, Hon-machi 1-chome, Kanazawa-shi, Ishikawa	Established April 1, 2005 Registered April 1, 2005
	21 6-5, Kawaramachi 3-chome, Chuo-ku, Osaka	Established April 1, 2005 Registered April 1, 2005
	22 1-7, Isobedori 3-chome, Chuo-ku, Kobe	Established April 1, 2005 Registered April 1, 2005
	23 1-3, Shimo-ishii 1-chome, Okayama	Established April 1, 2005 Registered April 1, 2005
	24 2-1, Shimokawabata, Hakata-ku, Fukuoka	Established April 1, 2005 Registered April 1, 2005
Equity warrant	First equity warrant Number of equity warrants: 1,410 Type and number of shares for equity warrants Common shares of the Company: 141,000 shares The number of shares of stock for one equity warrant (hereinafter referred to as the "number of granted shares") shall be 100 shares. In the event of a stock split or reverse stock split involving the common shares of stock of the Company, the number of granted shares shall be adjusted based on the following formula. Any fractional number of shares less than one share that will arise as a result of the adjustment shall be discarded. Number of granted shares after adjustment = number of granted shares before adjustment x ratio of stock split or reverse stock split When there is an unavoidable reason requiring the adjustment of the number of granted shares such as capital decrease, merger or company spin-off of the Company, the number of granted shares shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Issue price of one equity warrant Free Amount of money to be paid at the time of the exercise of each equity warrant The amount of money to be paid at the time of the exercise of each equity warrant shall be the amount obtained by multiplying the number	

of granted shares by the amount of money to be paid for one share to be issued or transferred through the exercise of each equity warrant (hereinafter referred to as the "exercise price").
The exercise price shall be the average of the closing prices (hereinafter referred to as the "closing price") of ordinary transactions of the Company's common shares at the Tokyo Stock Exchange for the days (excluding days when no transactions were carried out) of the month preceding the month that includes the date of issue of equity warrants (hereinafter referred to as the "issuing date"). Any fractional number of less than one yen shall be rounded up to one yen. However, if the exercise price is lower than the closing price on the issuing date (if there was no closing price on the issuing date, it shall be the closing price on the immediately preceding date), the said closing price shall become the exercise price.
When the Company issues new common shares or disposes of treasury stock at a price lower than market price (with the exception of the exercise of equity warrants and the conversion of convertible bonds based on the Commercial Code before the enforcement of the Law for Partial Amendment of the Commercial Code, etc. (No. 128 law of 2001)), the exercise price shall be adjusted based on the following formula. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.

Exercise price after adjustment = exercise price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares)

The "number of already issued shares" used for the above formula shall be the number of shares obtained by deducting the number of treasury stock held by the Company from the number of outstanding shares of the Company. When treasury stock is disposed of, the "number of newly issued shares" shall be read as the "number of disposed treasury shares."
In the event of a stock split or reverse stock split of the common shares of the Company on or after the issuing date, the exercise price shall be adjusted proportionately based on the ratio of the stock split or reverse stock split. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.
When there is an unavoidable reason requiring the adjustment of the exercise price such as capital decrease, merger or company spin-off of the Company on and after the issuing date, the exercise price shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc.
Period for the exercise of equity warrants:
From July 1, 2005 to June 27, 2013
Conditions for the exercise of equity warrants (excluding the amount of payment and period for exercise):
The partial exercise of each equity warrant shall not be allowed.
Reasons for the Company's cancellation of equity warrants and conditions for cancellation:
(i) When a proposal for the approval of a merger agreement under which the Company will not be the surviving company is approved at the general shareholders meeting of the Company, or a proposal for the approval of a stock exchange agreement or stock transfer based on which the Company will become a wholly-owned subsidiary is approved at the general shareholders meeting of the Company, the Company may cancel the equity warrants without

	consideration. (ii) The Company may cancel without consideration equity warrants acquired and held by the Company which were not yet exercised. Registered July 11, 2003
	Second equity warrant Number of equity warrants: 1,470 Type and number of shares for equity warrants Common shares of the Company: 147,000 shares The number of shares of stock for one equity warrant (hereinafter referred to as the "number of granted shares") shall be 100 shares. In the event of a stock split or reverse stock split involving the common shares of stock of the Company, the number of granted shares shall be adjusted based on the following formula. Any fractional number of shares less than one share that will arise as a result of the adjustment shall be discarded. Number of granted shares after adjustment = number of granted shares before adjustment x ratio of stock split or reverse stock split When there is an unavoidable reason requiring the adjustment of the number of granted shares such as capital decrease, merger or company spin-off of the Company, the number of granted shares shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Issue price of one equity warrant Free Amount of money to be paid at the time of the exercise of each equity warrant The amount of money to be paid at the time of the exercise of each equity warrant shall be the amount obtained by multiplying the number of granted shares by the amount of money to be paid for one share to be issued or transferred through the exercise of each equity warrant (hereinafter referred to as the "exercise price"). The exercise price shall be the average of the closing prices (hereinafter referred to as the "closing price") of ordinary transactions of the Company's common shares at the Tokyo Stock Exchange for the days (excluding days when no transactions were carried out) of the month preceding the month that includes the date of issue of equity warrants (hereinafter referred to as the "issuing date"). Any fractional number of less than one yen shall be rounded up to one yen. However, if the exercise price is lower than the closing price on the issuing date (if there was no closing price on the issuing date, it shall be the closing price on the immediately preceding date), the said closing price shall become the exercise price. When the Company issues new common shares or disposes of common treasury stock at a price lower than the market price on or after the issuing date (with the exception of the exercise of equity warrants, the conversion of convertible bonds based on the Commercial Code before the enforcement of the Law for Partial Amendment of the Commercial Code, etc. (No. 128 law of 2001) and the transfer of treasury stock based on the provision of Article 221-2 (request for sale of shares that are less than the number of shares in one stock trade unit) of the Commercial Code), the exercise price shall be adjusted based on the following formula. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen.

	Exercise price after adjustment = exercise price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The "number of already issued shares" used for the above formula shall be the number of shares obtained by deducting the number of treasury stock held by the Company from the number of outstanding shares of the Company. When treasury stock is disposed of, the "number of newly issued shares" shall be read as the "number of disposed treasury shares." In the event of a stock split or reverse stock split of the common shares of the Company on or after the issuing date, the exercise price shall be adjusted proportionately based on the ratio of the stock split or reverse stock split. Any fractional number of less than one yen arising from the adjustment shall be rounded up to one yen. When there is an unavoidable reason requiring the adjustment of the exercise price such as capital decrease, merger or company spin-off of the Company on and after the issuing date, the exercise price shall be reasonably adjusted in consideration of the conditions of capital decrease, merger or company spin-off, etc. Period for the exercise of equity warrants: From July 1, 2006 to June 24, 2014 Conditions for the exercise of equity warrants (excluding the amount of payment and period for exercise): The partial exercise of each equity warrant shall not be allowed. Reasons for the Company's cancellation of equity warrants and conditions for cancellation: (i) When a proposal for the approval of a merger agreement under which the Company will not be the surviving company is approved at the general shareholders meeting of the Company, or a proposal for the approval of a stock exchange agreement or stock transfer based on which the Company will become a wholly-owned subsidiary is approved at the general shareholders meeting of the Company, the Company may cancel the equity warrants without consideration. (ii) The Company may cancel without consideration equity warrants acquired and held by the Company which were not yet exercised. Registered July 7, 2004
Convertible corporate bond	Third unsecured convertible corporate bond Total amount of convertible bonds ¥14,921,000,000 ¥14,915,000,000 Changed April 30, 2001, and registered May 9, 2001 ¥14,913,000,000 Changed April 30, 2002, and registered May 10, 2002 ¥14,911,000,000 Changed May 31, 2002, and registered June 12, 2002 ¥14,903,000,000 Changed December 30, 2002, and registered January 14, 2003 Conditions for conversion: The issue price per share of the shares (the "conversion price") issued through conversion shall be decided as shown in (1) below, and the number of shares to be issued through conversion shall be as shown below. However, conversion shall not be requested for part of the face value of these bonds and interest.

*Dated numbers are underlined

	Number of shares = total of the face values of these bonds presented by each bond holder for the request of a conversion / conversion price In this event, if any fractional number of shares less than one share is created, the amount of the face value of bonds equivalent to the fractional number of shares shall be redeemed at a rate of 100 yen for the face value of 100 yen. (1) Conversion price: 4,413 yen (2) Adjustment of the conversion price If the company issues new shares at a paid amount which is lower than market price after the issue of these bonds, the conversion price shall be adjusted based on the following formula. Conversion price after adjustment = conversion price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The conversion price shall also be adjusted in the event of a stock dividend, free issue and stock split or reverse stock split. When, in the event of the issue of registered par value common shares of the company through conversion, the conversion price after adjustment is lower than the par value of the registered par value common shares of the company, the par value shall become the conversion price. Details of shares to be issued through conversion: Registered par value common shares of the company (par value per share: 50 yen) However, if the company decides that shares to be issued through the conversion of these bonds should be registered non-par-value common shares, the shares shall be registered non-par-value common shares of the company. Period for the request of conversion: From September 1, 1987 to December 30, 2002 Amount of each convertible bond: One million yen Amount of payment for each convertible bond: Full amount These bonds may be converted into shares.
	Expiration of the period for the request of conversion on December 30, 2002 Registered January 14, 2003
	Yen-denominated convertible bond to mature in 2014 Total amount of convertible bonds: ¥18,880,000,000 ¥18,680,000,000 Changed May 31, 1999, and registered June 14, 1999 ¥17,690,000,000 Changed June 30, 1999, and registered July 12, 1999 ¥11,230,000,000 Changed July 31, 1999, and registered August 10, 1999 ¥10,540,000,000 Changed August 31, 1999, and registered September 13, 1999 ¥9,650,000,000 Changed October 31, 1999, and registered November 12, 1999 ¥9,440,000,000 Changed November 30, 1999, and registered December 13, 1999 ¥9,220,000,000 Changed December 31, 1999, and registered January 14, 2000

	¥9,180,000,000 Changed January 31, 2000, and registered February 14, 2000 ¥8,390,000,000 Changed February 29, 2000, and registered March 14, 2000 ¥8,150,000,000 Changed April 30, 2000, and registered May 12, 2000 ¥8,140,000,000 Changed May 31, 2000, and registered June 13, 2000 ¥7,510,000,000 Changed July 31, 2000, and registered August 8, 2000 ¥7,290,000,000 Changed August 31, 2000, and registered September 11, 2000 ¥6,640,000,000 Changed November 30, 2000, and registered December 8, 2000 ¥6,610,000,000 Changed December 31, 2000, and registered January 12, 2001 ¥6,600,000,000 Changed January 31, 2001, and registered February 8, 2001 ¥6,500,000,000 Changed February 28, 2002, and registered March 11, 2002 ¥6,480,000,000 Changed May 31, 2002, and registered June 12, 2002 ¥6,470,000,000 Changed April 30, 2004, and registered May 13, 2004 ¥5,820,000,000 Changed October 31, 2004, and registered November 10, 2004 ¥5,020,000,000 Changed January 31, 2005, and registered February 8, 2005
	Conditions for conversion: These bonds may be converted into par value common shares of the Company at a rate of one par value common share of the Company for the following conversion price, based on the face amount of these bonds: However, any fractional number of shares less than one share created at the time of conversion shall be discarded, and no adjustment using cash shall be made. a. The initial conversion price shall be 1,979 yen per share. b. Revision of the conversion price When an amount obtained by multiplying the average closing price for 30 consecutive business days starting from 45 consecutive business days in which there is a closing price of ordinary transactions of the Company's par value common shares on the Tokyo Stock Exchange before March 31, 1998, March 31, 2004 and March 31, 2009, respectively, (hereinafter respectively referred to as the "determination date") by 1.025 (any fraction of less than one yen shall be rounded up to one yen) is lower by one yen or more than the conversion price effective on each determination date, on and after April 22, 1998, April 22, 2004, and April 22, 2009 (hereinafter respectively referred to as the "effective date"), respectively, the conversion price shall be changed to each amount calculated as above (subject, however, to the adjustment set out in c. below, which took effect between the determination date and a date prior to the effective date). However, as a result of the adjustment, the conversion price shall not be lowered to less than 50% of the initial conversion price (however, if adjusted as set out in c. below, it shall be the amount after adjustment). If the adjusted conversion price is less than 50% of the initial conversion price, the conversion price

Astellas Pharma Inc.
Company number 0199-01-034966
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo

	shall be the amount obtained by rounding up less than one yen of an amount equivalent to 50% of the conversion price to one yen. c. Adjustment of conversion price Where the Company issues new common shares at an amount for payment that is lower than the market price of the common shares of the Company after the issue of these bonds, the conversion price shall be adjusted based on the following formula: Conversion price after adjustment = conversion price before adjustment x (number of already issued shares + number of newly issued shares x amount of payment per share / market price) / (number of already issued shares + number of newly issued shares) The conversion price shall be adjusted appropriately in the event of a stock split, reverse stock split, issue of convertible bonds or bonds with warrants at the initial conversion price, a warrant exercise price that is lower than the market price of the common shares of the Company, or in other certain cases; provided, however, that the conversion price shall not be lower than the par value of the common shares of the Company. Details of shares to be issued through conversion: Par value common shares of the Company (current par value per share: 50 yen) Period for request of conversion: From May 9, 1994 to close of business on March 24, 2014 (based on the time of a place where conversion is requested) Amount of each convertible bond: 10 million yen Amount of payment for each convertible bond: Full amount These bonds may be converted into shares.
Company spin-off	Spinning-off into Zepharma Inc. at 7-1, Nihonbashi-Honcho 2-chome, Chuo-ku Tokyo on October 1, 2004 Registered October 1, 2004
Merger	Merged Fujisawa Pharmaceutical Co., Ltd at 4-7, Doshomachi 3-chome, Chuo-ku Osaka Registered April 1, 2005
Matters concerning the registered record	Based on the provision of Paragraph 3 of the supplementary regulation of the 1989 Ministerial Ordinance No. 15 of the Ministry of Justice Transfered May 20, 1999

This is to certify that the above are all the matters that are recorded on the register that are not sealed.

April 7, 2005
Tokyo Legal Affairs Bureau
Registrar Motoyuki Ohba

履歴事項全部証明書

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

商　号	山之内製薬株式会社	
	アステラス製薬株式会社	平成１７年　４月　１日変更 平成１７年　４月　１日登記
本　店	東京都中央区日本橋本町二丁目３番１１号	
公告をする方法	東京都において発行する日本経済新聞に掲載する	
貸借対照表に係る情報の提供を受けるために必要な事項	ｈｔｔｐ：／／ｗｗｗ．ｙａｍａｎｏｕｃｈｉ．ｃｏｍ／ｊｐ／ｉｎｄｅｘ．ｈｔｍｌ	平成１５年　３月２５日設定 平成１５年　４月　１日登記
	ｈｔｔｐ：／／ｗｗｗ．ａｓｔｅｌｌａｓ．ｃｏｍ／ｊｐ	平成１７年　４月　１日変更 平成１７年　４月　１日登記
会社成立の年月日	昭和１４年３月２０日	
目　的	１．医薬品、医薬部外品、動物用医薬品、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、飼料および飼料添加物、化粧品、衛生用具、医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．医療用機械器具、産業用機械器具、家庭用機器の製造、販売および輸出入 ４．酒精飲料および飲料品の製造、販売および輸出入 ５．実験動物の飼育・販売および輸出入 ６．不動産の売買、賃貸借、管理およびその仲介 ７．倉庫業および道路運送事業 ８．旅館業および保健体育施設の経営および管理 ９．損害保険代理業 １０．コンピューターによる情報処理サービス業 １１．前各号に付帯または関連する一切の事業	
	１．医薬品、医薬部外品、動物用医薬品、試薬、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、肥料、飼料および飼料添加物、化粧品、衛生用具、医療用具、動物用医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．天産物の売買ならびに輸出入 ４．医療用具の賃貸借および保守 ５．医療用機械器具、産業用機械器具、家庭用機器の製造、販売、輸出入、賃貸借および保守	

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	６．医療に関連する各種科学的検査 ７．酒類、酒精飲料および飲料品の製造、販売および輸出入 ８．実験動物の飼育・販売および輸出入 ９．不動産の売買、賃貸借、管理およびその仲介 １０．倉庫業、道路運送事業および貨物利用運送事業 １１．旅館業および保健体育施設の経営および管理 １２．損害保険代理業 １３．出版業 １４．コンピューターの販売、賃貸借および保守 １５．コンピューターのソフトウェアの開発、販売および賃貸借 １６．コンピューターによる情報処理・提供サービス業 １７．経営コンサルタント業 １８．前各号に付帯または関連する一切の事業 平成１７年　４月　１日変更　　平成１７年　４月　１日登記	
一単元の株式の数	１０００株	
	１００株	平成１４年　４月　１日変更 平成１４年　４月　２日登記
発行する株式の総数	８億株	
	２０億株	平成１７年　４月　１日登記
発行済株式の総数並びに種類及び数	発行済株式の総数 ３億６１１５万２５２２株	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	発行済株式の総数 ３億６１２０万３０５２株	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	発行済株式の総数 ３億６１２０万３６０４株	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	発行済株式の総数 ３億６１２１万４２６２株	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	発行済株式の総数 ３億６１２１万６４７０株	平成１４年１２月３０日変更 平成１５年　１月１４日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	発行済株式の総数 ３億６１２２万１５２３株	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	発行済株式の総数 ３億６１５４万９９７１株	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	発行済株式の総数 ３億６１９５万４２１５株	平成１７年　１月３１日変更 平成１７年　２月　８日登記
	発行済株式の総数 ５億７１４２万８００３株	 平成１７年　４月　１日登記
資本の額	金９９６億９４５６万３８４１円	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	金９９７億４４５６万３８４１円	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	金９９７億４５５６万３５１３円	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	金９９７億５６５６万３１８５円	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	金９９７億６０５６万１８７３円	平成１４年１２月３０日変更 平成１５年　１月１４日登記
	金９９７億６５５６万１８７３円	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	金１０００億９０５６万１８７３円	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	金１００４億９０５６万１８７３円	平成１７年　１月３１日変更 平成１７年　２月　８日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

名義書換代理人の氏名及び住所並びに営業所	東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社 東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社　本店 平成１２年１２月　４日変更	平成１２年１２月　８日登記
役員に関する事項	取締役　小野田正愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　竹中登一	平成１３年　６月２８日重任 平成１３年　７月１０日登記
	取締役　竹中登一	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　木村薫	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　柿谷宗敏	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　髙山暢二	平成１３年　６月２８日重任 平成１３年　７月１０日登記
	取締役　髙山暢二	平成１５年　６月２７日重任 平成１５年　７月１１日登記
		平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　河石清	平成１２年　６月２９日重任 平成１２年　７月１２日登記
		平成１４年　６月２７日退任 平成１４年　７月１０日登記
	取締役　上田英彦	平成１２年　６月２９日重任 平成１２年　７月１２日登記
	取締役　上田英彦	平成１４年　６月２７日重任 平成１４年　７月１０日登記
		平成１６年　６月２４日退任 平成１６年　７月　７日登記
	取締役　鈴木弘	平成１２年　６月２９日重任 平成１２年　７月１２日登記
		平成１４年　６月２７日退任 平成１４年　７月１０日登記
	取締役　能浦栄蔵	平成１２年　６月２９日重任 平成１２年　７月１２日登記
		平成１４年　６月２７日退任 平成１４年　７月１０日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目3番11号
アステラス製薬株式会社
会社法人等番号　0199－01－034966

取締役	井上雅勝	平成12年　6月29日重任 平成12年　7月12日登記 平成14年　6月27日退任 平成14年　7月10日登記
取締役	田村隼也	平成12年　6月29日重任 平成12年　7月12日登記
取締役	田村隼也	平成14年　6月27日重任 平成14年　7月10日登記
取締役	田村隼也	平成16年　6月24日重任 平成16年　7月　7日登記 平成17年　3月31日辞任 平成17年　4月　1日登記
取締役	市川邦英	平成12年　6月29日重任 平成12年　7月12日登記
取締役	市川邦英	平成14年　6月27日重任 平成14年　7月10日登記
取締役	市川邦英	平成16年　6月24日重任 平成16年　7月　7日登記 平成17年　3月31日辞任 平成17年　4月　1日登記
取締役	高橋重一	平成13年　6月28日重任 平成13年　7月10日登記
取締役	高橋重一	平成15年　6月27日重任 平成15年　7月11日登記 平成16年　6月24日辞任 平成16年　7月　7日登記

整理番号　ク604523　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　畑中和義	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　畑中和義	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　石井康雄	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　石井康雄	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　佐羽俊男	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　佐羽俊男	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　岸　功	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　岸　功	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　平岩廣章	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　平岩廣章	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　柳沢勲	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　柳沢勲	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
	取締役　柳澤勲	柳沢勲の氏
		平成１６年　３月１９日更正
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　臼田眞治	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　杉崎生弥	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　中島一	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　宮崎石基	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　吉長孝二	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　長谷川忠夫	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　松尾眞 （社外取締役）	平成１６年　６月２４日就任 平成１６年　７月　７日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　青木初夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　竹中登一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　田村隼也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　野木森雅郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　市川邦英	平成１７年　４月　１日就任 平成１７年　４月　１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目3番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　瀬島宏一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　児島章郎 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　松尾眞 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	千葉県流山市野々下三丁目９３１番地の３５ 代表取締役　小野田正愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１４年　６月２７日辞任 平成１４年　７月１０日登記
	千葉県流山市松ケ丘四丁目５０５番地の５６ 代表取締役　竹中登一 東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一 東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　３月１０日住所移転 平成１５年　３月１７日登記 平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	東京都中央区日本橋浜町二丁目３番２－１２０２号 代表取締役　上田英彦	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日退任 平成１６年　７月　７日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１６年１０月　１日就任 平成１６年１０月　１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	大阪府池田市畑四丁目１３番３号 代表取締役　青木初夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	大阪府高槻市真上町六丁目６５番２号 代表取締役　野木森雅郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　日巻洋之	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	監査役　佐々木典夫	平成１２年　６月２９日就任 平成１２年　７月１２日登記
	監査役　佐々木典夫	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　立川四郎	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	監査役　大谷豊達	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	監査役　大谷豊達	平成１６年　６月２４日重任 平成１６年　７月　７日登記
		平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　山田英夫	平成１３年　６月２８日就任 平成１３年　７月１０日登記
	監査役　山田英夫	平成１６年　６月２４日重任 平成１６年　７月　７日登記
	監査役　斎藤健一郎	平成１５年　６月２７日就任 平成１５年　７月１１日登記
	監査役　松尾眞	平成１５年　６月２７日就任 平成１５年　７月１１日登記
		平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	監査役　石井政弥	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　小林幹司	平成１７年　４月　１日就任 平成１７年　４月　１日登記
支　店	１ 東京都中央区日本橋本町二丁目４番７号	
	東京都中央区日本橋本町二丁目５番７号	平成１４年　９月２８日移転 平成１４年１０月　４日登記
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月２４日移転 平成１７年　２月　１日登記

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　１２／２１

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

2 大阪市中央区北浜三丁目７番１２号		
大阪市中央区瓦町三丁目６番５号	平成１５年　５月１９日移転 平成１５年　５月２１日登記	
3 北海道札幌市中央区大通西五丁目９番地１		
4 名古屋市中区栄一丁目１０番２１号		
名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日移転 平成１７年　４月　１日登記	
5 宮城県仙台市青葉区大町二丁目２番２５号		
6 福岡市博多区博多駅東一丁目１８番２５号		
福岡市博多区下川端２番１号	平成１７年　４月　１日移転 平成１７年　４月　１日登記	
7 東京都中央区日本橋本町二丁目５番６号		
東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記	
東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日移転 平成１７年　４月　１日登記	
8 香川県高松市寿町一丁目４番８号		
香川県高松市サンポート２番１号	平成１６年　３月２２日移転 平成１６年　３月２２日登記	
9 広島県広島市中区大手町三丁目７番２号		
広島市中区大手町二丁目１１番１０号	平成１７年　４月　１日移転 平成１７年　４月　１日登記	

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	１０ 台北市南京東路三段２８７号	平成１６年１０月３１日廃止 平成１６年１１月　１日登記
	１１ 横浜市中区太田町六丁目８４番地２	
	横浜市西区みなとみらい二丁目２番１号	平成１５年　２月２５日移転 平成１５年　３月　４日登記
	１２ 京都市中京区烏丸通二条下る秋野々町５１３番地	
	１３ 東京都中央区日本橋本町二丁目５番６号	
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
	さいたま市大宮区桜木町一丁目７番地５	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	１５ 仙台市青葉区大町二丁目２番２５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１６ 東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１７ 千葉市美浜区中瀬二丁目６番地	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１８ 東京都中央区日本橋本町一丁目５番９号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１９ 名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日設置 平成１７年　４月　１日登記

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	２０ 石川県金沢市本町一丁目５番２号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２１ 大阪市中央区瓦町三丁目６番５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２２ 神戸市中央区磯辺通三丁目１番７号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２３ 岡山市下石井一丁目１番３号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２４ 福岡市博多区下川端２番１号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
新株予約権	第１回新株予約権 新株予約権の数 １４１０個 新株予約権の目的たる株式の種類及び数 当社普通株式　１４万１０００株 新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。 なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。 調整後付与株式数　＝　調整前付与株式数　×　分割または併合の比率 また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。 各新株予約権の発行価額 無償	

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各新株予約権の行使に際して払込みをすべき金額
　各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
　行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
　なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使及び「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換の場合を除く。）次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

　上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
　また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
　さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
　平成１７年７月１日から平成２５年６月２７日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
　各新株予約権の一部行使はできないこととする。
会社が新株予約権を消却することができる事由及び消却の条件
　①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。
　②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。

平成１５年　７月１１日登記

第２回新株予約権
新株予約権の数
１４７０個

新株予約権の目的たる株式の種類及び数
当社普通株式１４万７０００株
新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。
なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。
調整後付与株式数＝調整前付与株式数×分割または併合の比率
また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。
各新株予約権の発行価額
無償
各新株予約権の行使に際して払込みをすべき金額
各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使、「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換及び商法第２２１条ノ２の規定（単元未満株式の売渡請求）に基づく自己株式の譲渡の場合を除く。）は、次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
平成１８年７月１日から平成２６年６月２４日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
各新株予約権の一部行使はできないこととする。

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	会社が新株予約権を消却することができる事由及び消却の条件 ①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。 ②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。 平成１６年　７月　７日登記
転換社債	第３回無担保転換社債 転換社債の総額 金１４９億２１００万円 金１４９億１５００万円 平成１３年　４月３０日変更　平成１３年　５月　９日登記 金１４９億１３００万円 平成１４年　４月３０日変更　平成１４年　５月１０日登記 金１４９億１１００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記 金１４９億３００万円 平成１４年１２月３０日変更　平成１５年　１月１４日登記 転換の条件 転換により発行する株式１株の発行価額（以下転換価額という。）は、下記(1)によって決定し、転換により発行すべき株式数は、次のとおりとする。ただし、本社債額面金額の一部及び利息については、転換を請求することはできない。 株式数＝各社債権者が転換請求のため提出した本社債額面金額の総額 ／ 転換価額 この場合に、１株未満の端数を生じたときは、その端数に相当する社債額面金額は、額面１００円につき１００円の割合で償還する。 (1)　転換価額　金４４１３円 (2)　転換価額の調整 転換価額は、当社が本社債発行後、時価を下回る払込金額で新株式を発行する場合には、次の算式により調整される。 調整後転換価額 ＝ 調整前転換価額 ×（既発行株式数＋新発行株式数×１株当りの払込金額／時価）／（既発行株式数＋新発行株式数） なお、株式配当、無償交付、株式の分割もしくは併合等が行われる場合にも調整されるものとする。ただし、転換により当社記名式額面普通株式を発行する場合で、調整後の転換価額が当社記名式額面普通株式の額面金額を下回るときは、当該額面金額を転換価額とする。 転換によって発行すべき株式の内容 当社記名式額面普通株式（１株の額面金額５０円） ただし、本社債の転換により発行する株式を当社記名式無額面普通株式とした場合は、当社記名式無額面普通株式。

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転換の請求をすることのできる期間
昭和６２年９月１日から昭和７７年１２月３０日まで
各転換社債の金額
金１００万円
各転換社債につき払い込んだ金額
全額
本社債はこれを株式に転換することができる

平成１４年１２月３０日転換請求期間満了　　平成１５年　１月１４日登記

２０１４年満期円貨建転換社債
転換社債の総額
金１８８億８０００万円
金１８６億８０００万円　平成１１年　５月３１日変更　平成１１年　６月１４日登記
金１７６億９０００万円　平成１１年　６月３０日変更　平成１１年　７月１２日登記
金１１２億３０００万円　平成１１年　７月３１日変更　平成１１年　８月１０日登記
金１０５億４０００万円　平成１１年　８月３１日変更　平成１１年　９月１３日登記
金９６億５０００万円　平成１１年１０月３１日変更　平成１１年１１月１２日登記
金９４億４０００万円　平成１１年１１月３０日変更　平成１１年１２月１３日登記
金９２億２０００万円　平成１１年１２月３１日変更　平成１２年　１月１４日登記
金９１億８０００万円　平成１２年　１月３１日変更　平成１２年　２月１４日登記
金８３億９０００万円　平成１２年　２月２９日変更　平成１２年　３月１４日登記
金８１億５０００万円　平成１２年　４月３０日変更　平成１２年　５月１２日登記
金８１億４０００万円　平成１２年　５月３１日変更　平成１２年　６月１３日登記
金７５億１０００万円　平成１２年　７月３１日変更　平成１２年　８月　８日登記
金７２億９０００万円　平成１２年　８月３１日変更　平成１２年　９月１１日登記
金６６億４０００万円　平成１２年１１月３０日変更　平成１２年１２月　８日登記
金６６億１０００万円　平成１２年１２月３１日変更　平成１３年　１月１２日登記
金６６億円　平成１３年　１月３１日変更　平成１３年　２月　８日登記
金６５億円　平成１４年　２月２８日変更　平成１４年　３月１１日登記
金６４億８０００万円　平成１４年　５月３１日変更　平成１４年　６月１２日登記

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アステラス製薬株式会社
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	金６４億７０００万円 平成１６年　４月３０日変更　　平成１６年　５月１３日登記 金５８億２０００万円 平成１６年１０月３１日変更　　平成１６年１１月１０日登記 金５０億２０００万円 平成１７年　１月３１日変更　　平成１７年　２月　８日登記 転換の条件 本社債は、その額面金額に対し、下記の転換価額につき当社額面普通株式１株の割合をもって当社額面普通株式に転換することができる。 但し、転換の際に生じる１株未満の端数は、これを切り捨て、現金による調整は原則として行わない。 イ．当初の転換価額は、１株当り金１９７９円とする。 ロ．転換価額の修正 １９９８年３月３１日、２００４年３月３１日及び２００９年３月３１日（以下それぞれ「決定日」という。）より東京証券取引所における当社額面普通株式の普通取引の終値のある４５連続営業日前に開始する３０連続営業日における終値の平均値に１．０２５を乗じ１円未満を切り上げた額が、当該各決定日に有効な転換価額を１円以上下回る場合には、転換価額は１９９８年４月２２日、２００４年４月２２日及び２００９年４月２２日（以下それぞれ「効力発生日」という。）以降、上記により算出された各金額（但し、決定日から効力発生日の前日までに効力の発生した下記ハ．の調整を受ける。）に修正されるものとする。但し、転換価額は、かかる修正の結果として当初の転換価額（但し、下記ハ．の調整がなされた場合には、調整後の金額）の５０％未満に修正されることはなく、５０％未満となる場合は、かかる転換価額の５０％にあたる金額の１円未満を切り上げた価額とする。 ハ．転換価額の調整 転換価額は、当社が本社債発行後、当社の普通株式の時価を下回る払込金額で新たに普通株式を発行する場合、次の算式により調整される。 $$\text{調整後転換価額} = \text{調整前転換価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新発行株式数} \times \text{１株当り払込金額}}{\text{１株当り時価}}}{\text{既発行株式数} + \text{新発行株式数}}$$ 又、転換価額は、株式の分割・併合、当社の普通株式の時価を下回る当初転換価額又は新株引受権行使価額での転換社債又は新株引受権付社債の発行その他一定の場合にも適宜調整される。但し、転換価額は当社額面普通株式の額面金額を下回らないものとする。 転換によって発行すべき株式の内容 当社額面普通株式（現在の１株の額面金額５０円） 転換の請求をすることのできる期間 １９９４年５月９日から２０１４年３月２４日の営業終了時（転換請求地時間）までとする。 各転換社債の金額 金１０００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる。

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。　　２０／２１

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
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会社分割	平成１６年１０月１日東京都中央区日本橋本町二丁目７番１号ゼファーマ株式会社に分割 平成１６年１０月　１日登記
吸収合併	大阪市中央区道修町三丁目４番７号藤沢薬品工業株式会社を合併 平成１７年　４月　１日登記
登記記録に関する事項	平成元年法務省令第１５号附則第３項の規定により 平成１１年　５月２０日移記

これは登記簿に記録されている閉鎖されていない事項の全部であることを証明した書面である。

平成１７年　４月　７日

東京法務局
登記官　　大　庭　元　行

整理番号　ク６０４５２３　　＊　下線のあるものは抹消事項であることを示す。